



# THE UNIVERSITY *of* EDINBURGH

This thesis has been submitted in fulfilment of the requirements for a postgraduate degree (e.g. PhD, MPhil, DClinPsychol) at the University of Edinburgh. Please note the following terms and conditions of use:

This work is protected by copyright and other intellectual property rights, which are retained by the thesis author, unless otherwise stated.

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge.

This thesis cannot be reproduced or quoted extensively from without first obtaining permission in writing from the author.

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the author.

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given.

**Identifying barriers to clinical trial participation with families affected by fragile  
X syndrome**

**By**

**Sarah Elizabeth Anne Eley**

MSc (by research) Degree  
University of Edinburgh  
2017

## Table of contents

List of tables and figures .....	1
List of Appendices .....	2
Declaration.....	3
Acknowledgements.....	4
Funding sources .....	5
Author contributions .....	6
Abstract.....	7
Chapter 1: Fragile X syndrome; current treatments and theories.....	11
History.....	12
Clinical features.....	14
Learning difficulties and behavioural features .....	15
Theories for treatment .....	17
Minocycline.....	17
Arbaclofen.....	18
Lovastatin.....	18
Acamprosate .....	19
mGluR5 Theory .....	20
Summary .....	21
Chapter 2: Barriers to clinical trial participation.....	22
Clinical Trials .....	23
General trial barriers.....	23
Intellectual disability trial barriers .....	24
Fragile X syndrome trial barriers.....	26
Chapter 3: Experiment .....	28
Introduction .....	29
Aims .....	29
Research design .....	30
Quantitative methodology.....	30
Qualitative methodology .....	31
Phenomenology .....	31
Methods.....	32

Recruitment .....	32
Ethical considerations .....	32
Identification/ approach .....	33
Questionnaire .....	34
Focus groups .....	35
Focus group topic guide .....	37
Rigour .....	37
Credibility .....	38
Transferability .....	38
Reflexivity .....	39
Data management .....	39
Data Analysis .....	40
Quantitative analysis .....	40
Qualitative analysis .....	40
Chapter 4: Findings .....	42
Questionnaires .....	43
Focus groups .....	49
Theme 1 Trial challenges/ barriers .....	51
Theme 2 Strategies to assist participation .....	56
Theme 3 motivating factors .....	60
Chapter 5: Summary, discussion and future directions .....	62
Discussion .....	63
Barriers .....	63
Overcoming barriers .....	67
USA vs UK .....	69
Implications .....	70
Strengths and limitations .....	71
Future directions .....	72
Conclusion .....	73
References .....	74
Appendix 1: Questionnaire .....	82
Appendix 2: Information sheet .....	87
Appendix 3: topic guide .....	90

## **List of tables and figures**

### **Tables**

Table 1: USA vs UK barriers

Table 2: Barriers and willingness to participate

Table 3: focus group attendance

### **Figures**

Figure 1: Fragile X Chromosome

Figure 2: mGluR Theory diagram

Figure 3: Response map

Figure 4: Link to FXS

Figure 5: Previously taken part in a clinical trial

Figure 6: Experience

Figure 7: Would take part in a future trial

Figure 8: Barriers

Figure 9: Thematic map

## **List of Appendices**

Appendix 1: Questionnaire

Appendix 2: Information sheet

Appendix 3: Topic guide

## **Declaration**

I certify that this project has been composed by me personally and that all work contained herein is my own, except where clearly indicated.

I certify that this work has not been submitted for any other degree or professional qualification.

I hereby grant the University of Edinburgh the right to publish this project, and to authorise its publication for any scholarly purpose with proper acknowledgement of authorship.

**Sarah Eley**

**February 2017**

## **Acknowledgements**

Firstly, I would like to thank the participants for so generously giving up their own time and effort, without which this study would not have been possible.

I would also like to thank the Fragile X Society for their assistance with recruitment without whose help this project would not have been possible.

I would like to particularly thank my supervisor for this project Dr Andrew Stanfield who provided invaluable support and guidance. In addition, Dr Andrew McKechnie and Dr Sue Fletcher-Watson.

Thank you to the Division of Psychiatry at the University of Edinburgh for giving me the financial support to undertake further study giving me the opportunity to produce this thesis.

Finally my gratitude goes out to my husband Ewan Eley and our families. It is no exaggeration to say that without their encouragement and support this work would not have been achieved.



## **Funding sources**

This work was funded by a Seedcorn grant from the Patrick Wild Centre.

Further focus group funding was awarded from Edinburgh Neuroscience neuroresearchers fund.

## **Author contributions**

1. Study design
2. NHS Lothian ethics application
3. Questionnaire design and dissemination
4. Organisation of focus groups
5. Facilitation of focus groups
6. Analysis of data

## **Abstract**

Fragile x syndrome (FXS) is thought to be the most common inherited form of intellectual and developmental disability and the most common known single gene cause of autism. The prevalence of FXS is approximately 1.4 per 10,000 males and 0.9 per 10,000 females. Learning difficulties in people with FXS can vary from mild to severe however it is most common to be within the mild to moderate range, with males often more affected than females. The current medical treatments for FXS are primarily symptomatic in nature; and include the use of selective serotonin reuptake inhibitors for anxiety, stimulants for attention deficit hyperactivity disorder and antipsychotics for irritability or aggressive behaviour. However, our understanding of FXS has now progressed to a stage where treatments selected to target the underlying neurobiology are now being trialled. Experience conducting research studies at The Patrick Wild Centre into this condition has suggested that some families are reluctant to take part in clinical trials making recruitment challenging. Therefore, this study was designed to understand barriers to participation specifically amongst patients with the condition and their families.

The primary aim of this study was to identify the barriers to research participation. The second aim of the study was to find out how barriers to clinical trial participation could be overcome in order to maximise recruitment for future studies. A mixed method design was used to collect both quantitative and qualitative data. Participants were identified from the UK Fragile X Society mailing list by a member of the Fragile X Society, The Patrick Wild Centre mailing list and through advertisements on the Patrick Wild Centre website, Facebook and Twitter feeds. A quantitative questionnaire was completed by 328 parents, carers, family members of individuals with FXS or by individuals with FXS. Following this, three focus groups took place in Chelmsford, Bristol and Edinburgh.

This study demonstrated that there are many different factors which may negatively influence motivation to participate in a clinical trial in this group. However, the main barriers to participation were concerns about possible side effects, travel, requirement for blood tests and financial reasons. When these were explored further during focus groups it was evident that these barriers were not as clear as they may have appeared and had many complexities to them. The main way to overcome barriers that was repeatedly discussed in each focus group was the importance of accessible information in helping families to understand the study including any potential safety issues. This study highlights that while there is no one thing that researchers can do that will work for everyone, there are many things that researchers can do to improve participation such as making their research more individual, flexible and accommodating.

### Lay summary

Fragile x syndrome (FXS) is thought to be the most common genetic cause of intellectual and developmental disability and an important cause of autism. It is thought that it occurs in 1.4 per 10,000 males and 0.9 per 10,000 females. Learning difficulties in people with FXS can vary from mild to severe however they are most commonly within the mild to moderate range, with males often more affected than females. The current medical treatments for FXS are primarily to treat symptoms related to the disorder, as opposed to being targeted at the underlying cause of the condition. However, our understanding of FXS has now progressed to a stage where treatments selected to target the underlying cause are now being trialled. Participation in clinical trials of new medicines for the condition are essential to determine whether these treatments are actually effective. Experience conducting research studies at The Patrick Wild Centre into this condition has suggested that some families are reluctant to take part in clinical trials making recruitment challenging. Therefore, this study was designed to understand barriers to participation specifically amongst patients with the condition and their families.

The primary aim of this study was to identify the barriers to research participation in order to maximise recruitment for future studies. The second aim of the study was to find out how barriers to clinical trial participation could be overcome. Questionnaires and focus group interviews were used to address these aims. A quantitative questionnaire was completed by 328 parents, carers, family members of individuals with FXS or by individuals with FXS. Following this, three focus groups took place in Chelmsford, Bristol and Edinburgh. Participants were identified from the UK fragile X society mailing list by a member of the Fragile X Society, The Patrick Wild Centre mailing list and the questionnaire was advertised on the Patrick Wild Centre website, Facebook and Twitter feeds.

This study clearly demonstrated that there are many different reasons for not taking part in clinical trials of medications. However, the main barriers to participation were

concerns about possible side effects, travel, requirement for blood tests and perceived or real financial reasons. When these barriers were explored further during focus groups it was evident that these barriers were not as clear as they may have appeared and had many complexities to them. The main way to overcome barriers that was repeatedly discussed in each focus group was the importance of accessible information in helping families to understand the study including any potential safety issues. This study highlights that there is no one thing that researchers can do that will work for everyone, and that they must look at ways to make their research more individual, flexible and accommodating.

## **Chapter 1: Fragile X syndrome; current treatments and theories**

## History

Fragile X Syndrome (FXS) was first discovered in 1943 by James Martin and Julia Bell who found a form of mental disability which was linked to the X chromosome (Martin and Bell, 1943). A chromosomal test was then developed in 1969 by Herbert Lubs who observed a constriction on the end of the long arm of the X chromosome giving a 'fragile' appearance (figure 1) , thus giving rise to the name 'Fragile X Syndrome' (Lubs, 1969). It was not until the late 1970's that testing for the condition became widely used when Grant Sutherland found a way to detect the 'fragile' site which led to the first diagnostic test for the condition (Sutherland and Hecht, 1985). At this time little was understood about the inheritance of this disorder as it was not typical of other X linked conditions, in that there were reports of unaffected males transmitting a mutation to their daughters. In 1985 Stephanie Sherman studied the inheritance pattern more closely which lead to the suggestion that the syndrome was a two-step process; the first step being a 'premutation' where there are no clinical symptoms present but which conferred increased risk of a symptomatic child, and the second mutation being a 'full mutation' for which symptoms are characteristic of FXS.

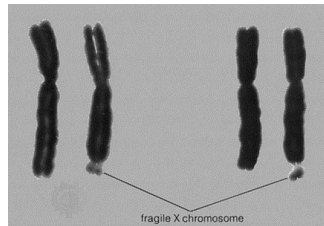
In 1991 a team of scientists sequenced the gene at the constricted part of the X chromosome and identified an expanded triplet (CGG) repeat sequence in the promotor region, which caused fragile X syndrome. They named the gene *FMR1*. The expansion of the CGG repeat sequence in the promotor region silences the gene, preventing its transcription and subsequent translation into the Fragile X Mental Retardation Protein (FMRP) resulting in the characteristic features of FXS (Verkerk et al., 1991).

FMRP, which is an RNA binding protein, is widely expressed, predominantly within brain neurons. Here it binds to RNA through its three binding domains. FMRP binds to target mRNAs to repress translation during transport to postsynaptic dendritic spines (Levenga et al., 2010). FMRP is essential for proper synaptic plasticity, neuronal



morphology and cognitive development, therefore its absence leads to varying levels of intellectual disability. Due to the location of the FMR1 gene and the presence of a second unaffected X chromosome females are typically less affected than males (Crawford et al., 2001).

Figure 1: Fragile X Chromosome (Figure adapted from encyclopedia britania)



FXS is thought to be the most common inherited form of intellectual and developmental disability and the most common known single gene cause of autism (Hagerman et al., 2010). However, the heterogeneity of FXS has historically made diagnosis challenging and the variation of symptom severity especially when comparing males and females adds to the difficulty in assessing prevalence. Prior to 1991 clinical diagnosis was made by carrying out mental and physical examinations alongside cytogenetic testing, a method which Sofocleous et al. (2009) have argued is much less reliable than the most up to date approach which uses a polymerase chain reaction (PCR) based technique and Southern blotting. A systematic review published in 2014 (Hunter et al., 2014) has reported that the prevalence of individuals with a full mutation is 1.4 per 10,000 males and 0.9 per 10,000 females. The number of people with a premutation was 11.7 per 10,000 in males and 34.4 per 10,000 in females. These numbers are lower than a previous systematic review which was carried out 10 years previously (Song et al., 2003), which highlights the difficulty to date in acquiring an accurate record of patients affected by the condition.

Individuals who are premutation carriers usually have normal IQ. Males may be more likely to display attentional problems, executive dysfunction, social deficits and obsessive compulsive behaviours (Farzin et al., 2006). Some male premutation carriers over the age of 50 develop neurologic deficits previously thought to have been parkinsonism; it is now recognised as fragile X-associated tremor/ataxia syndrome (FXTAS) (Jacquemont et al., 2004). Female permutation carriers are more likely to experience premature ovarian failure (Allingham-Hawkins et al., 1999, Campbell et al., 2016).

### **Clinical features**

The phenotypes associated with the full mutation syndrome vary considerably among patients. These can include; prominent forehead, narrow face, protruding ears, high arched palate, strabismus, macro-orchidism, low IQ, and connective tissue dysplasia including hyperflexibility of the joints (Hagerman and Hagerman, 2002, 2014, Kidd et al., 2014). The physical characteristics of FXS are often fairly subtle so often testing is carried out after failure to meet developmental milestones such as mild motor and/or language delays (Maes et al., 2000). Autistic like behaviours are also considered when looking for a diagnosis; commonly these include features such as hand biting, hand flapping and poor eye contact (Garber et al., 2008). Concurrent medical conditions associated with the condition are usually relatively mild, they include; gastroesophageal reflux disease, seizures and mitral valve regurgitation (Hagerman and Hagerman, 2002).

Autopsy studies have suggested that while the brains of people with FXS appear grossly unaffected, dendritic spines are longer and immature in appearance (Irwin et al., 2001). Elongated dendritic spines, a major site of synaptic transmission on cortical neurons, have been associated with intellectual disability, including in Down syndrome and Rett syndrome (Kaufmann and Moser, 2000). For this reason it is likely

that many aspects of FXS can be accredited to altered synaptic development and plasticity.

### **Learning difficulties and behavioural features**

Learning difficulties in people with FXS can vary from mild to severe however it is most common to be within the mild to moderate range of intellectual disability, with males often more affected than females. Around 60% of females with a full mutation will have some form of learning disability. Difficulties with learning include; problems with creative thinking, poor hand eye coordination, sequential processing, creative problem solving, visual motor planning and problems with short term memory (Hodapp et al., 1990). Often there are problems with receptive language so understanding can be much greater than that which might be indicated from the level of expressive language (Turk, 2011). There are inevitably problems with speech. Speech is often delayed and distorted and commonly displays echolalia, perseveration, cluttering and dysarthria (Sabaratnam, 2006).

Attentional problems and restlessness can be present in anyone with FXS with any degree of learning disability and can severely impair their ability to learn or engage with a task. Behavioural features include: restlessness, impulsivity, over activity, difficulty waiting, difficulty focusing on tasks, easily distracted and difficulty with transitions (Tsiouris and Brown, 2004). Common behavioural symptoms displayed by those affected by FXS are also often similar to those affected by Autism Spectrum Disorder (ASD), with around 30-50% meeting criteria for an ASD diagnosis. This would suggest, as argued by (Devitt et al., 2015), that autistic symptoms may be under genetic control. It has been shown that there are noticeable developmental patterns of adaptive behavioural function which shows a relative downward trajectory in those with FXS compared to their peers during childhood resulting in them falling further behind (Klaiman et al., 2014).

Anxiety is one of the most prevalent characteristics of FXS (Cordeiro et al., 2011). It decreases the ability for the individual to think clearly, adapt to situations and carry out everyday tasks causing shyness and upset by novel people or environments (Reiss and Freund, 1992). There are two main types of anxiety in FXS; anticipatory anxiety and social anxiety. If a person with FXS has previous experience of a situation they may be fearful in the future if it was unpleasant, thus causing anxiety due to learned experience. Individuals with FXS tend to display symptoms of social anxiety rather than social indifference. In social settings common features displayed are; gaze avoidance, self-injury, repetitive behaviours such as hand flapping, mood swings, challenging behaviour, emotional difficulties, difficulty initiating and maintaining friendships and insistence on routine. Scientists have tried to measure social anxiety in FXS by looking at mice to find out whether this is caused by the loss of *FMR1* (Spencer et al., 2005, Spencer et al., 2008). Their conclusions demonstrated that mice had normal levels of social interest and social recognition; however they showed high levels of social anxiety, suggesting that the loss of *FMR1* gene function results in altered anxiety and social behaviour (Spencer et al., 2005, Spencer et al., 2008).

Many people with FXS have sensory processing and integration problems (Hagerman and Hagerman, 2002, Riley, 2011). The most troubling feature of FXS reported is sensory based hyperarousal (Reiss and Hall, 2007). Often individuals may struggle to manage information if more than one sense is activated at the same time, causing them to feel overwhelmed and become upset or anxious. This in turn can lead to difficult or repetitive behaviours due to poor adaptability and coping. The feeling of being overwhelmed occurs as a result of deficits in sensory-motor gating which causes difficulty filtering auditory stimuli (Yuhas et al., 2011). There are two main categories for sensory problems; sensory discrimination and sensory modulation both of which individuals with FXS are likely to experience resulting in difficulties in learning and skill development (Baranek et al., 2002). Individuals with FXS tend to become hyperaroused by normal or excessive sensory information. Hyperarousal is associated

with an increase in the autonomic nervous system and heightened sympathetic arousal meaning that in individuals with FXS there is a lower threshold for responding to sensory and emotional stimuli.

### **Theories for treatment**

The current medical treatments for FXS are primarily symptomatic in nature; and include the use of selective serotonin reuptake inhibitors for anxiety, stimulants for attention deficit hyperactivity disorder and antipsychotics for irritability or aggressive behaviour. However, our understanding of FXS has now increased to a stage where treatments selected to target the underlying neurobiology are now being trialled. Whilst these appear to be successful in mice they have however failed to benefit patients with FXS. Efficacy has been demonstrated in one controlled trial of minocycline (Hagerman and Polussa, 2015) and potentially also arbaclofen (Berry-Kravis et al., 2012). There have also been some open label trials which have shown acamprosate and lovastatin to be of some varying benefit to individuals with FXS (Caku et al., 2014, Erickson et al., 2010, Erickson et al., 2013).

### ***Minocycline***

Minocycline is a commonly used antibiotic traditionally used for the treatment of acne. Minocycline is also an inhibitor of an enzyme called matrix metalloproteinase 9 (MMP-9). MMP-9 has been found to be overactive in FXS and is thought to be involved in synaptic plasticity (Szklarczyk et al., 2002) thus impacting on memory and learning (Bilousova et al., 2009). To the author's knowledge there has only been one randomised controlled trial of minocycline in fragile X syndrome (Leigh et al., 2013). This trial was a crossover design with participants allocated to 3 months treatment with either minocycline or placebo and a beneficial effect of minocycline was seen on one of the primary outcome measures; no effects on secondary outcome measures

were observed (Leigh et al 2013). This is consistent with the idea that minocycline has an effect in FXS by inhibiting the enzyme MMP-9. The same group later reported that the improvements observed were correlated with reductions in MMP-9 activity (Dziembowska et al., 2013).

### *Arbaclofen*

Arbaclofen (the (R)-isomer of racemic baclofen, a readily available anti-spasmodic medicine) showed initial promise. Arbaclofen is a GABA-B agonist, hypothesised to be of benefit to people with FXS both directly, by increasing GABAergic inhibition, and indirectly, through downstream effects on glutamate signalling (D'Hulst and Kooy, 2007). There has only been one published trial of arbaclofen in people with FXS to the author's knowledge. This was a crossover design, randomised placebo, controlled study where participants received the maximum dose of arbaclofen for a period of 4 weeks (Berry-Kravis et al., 2012) The study failed to show a significant effect of arbaclofen on the primary outcome measure, however it did report a number of beneficial effects on secondary and post hoc measures. Following on from this a larger Phase III trial of arbaclofen was conducted in FXS with an 8 week treatment period. Again however no significant benefit of the medication was shown on the primary outcomes and its development has been subsequently halted. Detailed results of this study have not yet been published.

### *Lovastatin*

Lovastatin is licenced as a drug that is widely used to help lower cholesterol. It is a HMG-CoA reductase inhibitor. It is believed that Lovastatin can correct cognitive deficits by reducing activation of the Ras-ERK intracellular pathway through interfering with the Ras and cell membrane interaction process and in doing so,

prevent the pathological changes in FXS that cause excessive protein synthesis. One study which looked at enhanced activity of the Ras pathway in FXS in an *FMR1* knockout mouse (Osterweil et al., 2013) found that lovastatin was able to correct the excessive Ras activity and block the mGluR5 mediated epileptiform activity. Lovastatin was found as a result of this to reduce hyper excitability in the visual cortex of the knockout mouse. An open label trial of Lovastatin in children with FXS where 15 people were treated with escalating doses for three months (Caku et al., 2014) has shown positive results. This trial showed the drug was well tolerated with minimal side effects and significant improvement was demonstrated in both the primary and secondary outcome measures in twelve out of the fifteen people who took part. A larger randomised controlled trial would be required in order to obtain efficacy of the treatment before this drug could be licenced for use in FXS.

### *Acamprosate*

Acamprosate is predominantly used to help maintain abstinence from alcohol in adults with alcohol dependency. It has the ability to bind to NMDA glutamate receptors (Hagerman and Polussa, 2015). Two studies have been carried out (Erickson et al., 2010, Erickson et al., 2013) trialling Acamprosate in FXS. The first – an open label study in three adults demonstrated improvements in both clinical global impression scale (CGI-I) measurements and in language. The second – a ten week open label trial in twelve children demonstrated improvements in CGI-I, social behaviour, inattention/hyperactivity and reductions in social impairment. Blood tests showing levels of plasma brain derived neurotropic factor also showed an increase after treatment with Acamprosate, however this was not in correlation with treatment response measures. A phase II multi centre double blind placebo controlled trial has taken place in America results of which will not be known until later on in 2017.

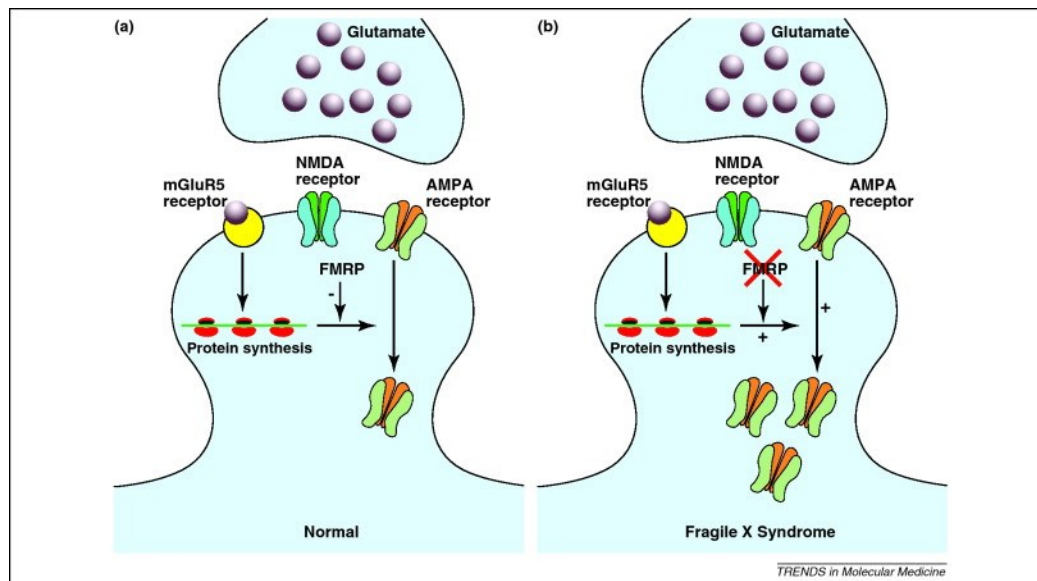
### *mGluR5 Theory*

A novel connection between metabolic glutamate receptor (mGluR) signalling and the fragile X phenotype was discovered in 2002 when it was shown that mGluR activity is significantly increased in the hippocampus of animals lacking FMRP (Huber et al., 2002).

The mGluR theory explains the immature synaptic connections seen in both animal models and humans and is the leading theory regarding the pathophysiology of FXS (Bear et al., 2004) (figure 2). The mGluR5 theory is that the lack of FMRP leads to excess mGluR mediated protein translation in the synapse. In turn this leads to changes in synaptic plasticity, in particular increased hippocampal long term depression. This then predicts that reducing mGluR5 activity will reverse the excess protein translation and restore the synaptic phenotype. It was this theory which led to the development of mGluR5 antagonists as a treatment for FXS. When tested in animal models significant rescue of many phenotypes was shown, however when used in human trials efficacy criteria have not yet been met (Pop et al., 2014, Hagerman et al., 2012, Berry-Kravis et al., 2016)



**Figure 2. The mGluR Theory (Levenga et al., 2010)**



### *Summary*

Having discussed what FXS is and the current theories for treatment options, it is apparent that not enough is known about how the condition can be treated in order to provide a better quality of life for people. Whilst some treatments have appeared successful in mice models there has been a disparity when the theory is translated to humans and many treatments options still require further testing e.g. lovastatin and minocycline. There are also other medications that are being considered that require testing e.g. alcobra and cannabinoids. It is important, research, specifically clinical trials, are carried out in order to find out more. If sufficient numbers of participants cannot be sought for these trials then clinicians are less likely to fund or use interventions (Oliver et al., 2002). Specifically, if numbers of participants of underrepresented minorities (such as people with intellectual disabilities) are not obtained for clinical trials there is a danger that existing health disparities will be increased. The NHS plan (Department of Health 2000) committed to including more people with learning disabilities in participating in research, so it is important to make sure these trials take place.

## **Chapter 2: Barriers to clinical trial participation**

## **Clinical Trials**

A clinical trial is any study which assigns participants or groups of participants to a specific health related intervention to measure and evaluate the effects on health outcomes according to a research protocol. Interventions can be drugs, devices or procedures. Often a comparison is made between a new approach and an existing already available one, or to a placebo. Clinical trials are conducted in order to ensure safety and efficacy of new treatments or interventions. They are performed so that medical knowledge can be added upon and treatment, diagnosis and prevention of diseases and conditions can be better understood. Adequate inclusion of participants in clinical trials is essential in order to ensure development and improvement in all areas of healthcare (Chalela et al., 2014). Without adequate representation in clinical trials it is impossible to assess differential effects or to ensure generalizability to trial outcomes (Ford et al., 2005). It is therefore important that efforts are made to include people by identifying barriers, despite these often being complex, and doing all that can be done to address these.

### **General trial barriers**

While there are few papers that examine the barriers specifically related to FXS it can be helpful to look at barriers to research participation in general. A systematic review by (Ross et al., 1999) found that there were five main categories for barriers to recruitment in randomised controlled trials for patient participation. These were:

- Additional demands
- Additional appointments and procedures
- Causing discomfort or inconvenience
- A strong preference for or against a particular treatment e.g. not wanting to take experimental medication or take placebos
- Patients found uncertainty to be difficult

Additionally information and informed consent were concerns as people wanted more information. The review concluded that to overcome barriers, study demands should be kept to a minimum and patients should be supported throughout their decision whether or not to take part in a clinical trial.

More recently barriers and promoting factors to participate in early stage clinical trials were examined in one study (Chalela et al., 2014) which found the main barriers to be socio economic, distrust of the medical system, fear/uncertainty and fantastic/spiritual beliefs. Factors promoting participation were potential symptom improvement, disease control, high quality medical care, hopefulness and social influences.

A further recent review to identify strategies to address barriers to clinical trial participation (Heller et al., 2014) found combined strategies to be the most useful. These included; spending time before protocol design developing recruitment strategies, engaging with medical professionals, gaining community trust, onsite meetings within busy community practices to increase provider engagement, community education about clinical trials, transport assistance and offering more flexible hours.

### **Intellectual disability trial barriers**

It is well known that the health of people with intellectual disability is often poor and numbers for participation in research studies in this population can be difficult to achieve (Gilbert, 2004, Lennox et al., 2005). A review highlighting the difficulties in conducting a randomised controlled trial of health service interventions in intellectual disability highlighted three main concerns; ethical, methodological and service capacity (Oliver et al., 2002), which echoes the results from the systematic review by

(Ross et al., 1999), that barriers to participation not only arise from a lack of people participating but rather there are additional barriers with regards to clinician participation. Both clinicians and services require time and additional support to recruit people for clinical trials. Concerns about altering the clinician/patient relationship act as barriers towards the facilitation of research and require addressing. This research is further reiterated in a report (Lennox et al., 2005) which breaks down barriers in recruitment to intellectual disability research into two main categories, sectoral and research process. Sectoral barriers refer to a lack of accessibility to people and funding constraints, while research process barriers refer to study specific difficulties and ethical considerations. Ethical concerns were also perceived to be a major barrier to recruitment to a medication trial (Oliver-Africano et al., 2010), alongside other barriers including refusal to give consent, refused tablets, side effects, and primary carer antagonistic towards clinical trials.

Prior to the 1960's there is no evidence of inclusive research in learning disabilities. Rather, those with learning disabilities were tested or observed but their views were never asked (Walmsley, 2001). Historically research with people with learning disabilities has been more *research on*, rather than *research with*, carried out by detached researchers, deciding on research questions and developing what they feel to be suitable measures (Kiernan, 1999). "*Advances in the social position of people with learning disabilities have led to a situation where research and evaluation studies are increasingly required to include the views and opinions of people with learning disabilities*" (Gilbert, 2004). Both funders and ethical committees have begun to stress the importance of patient and public involvement. Gilbert (2004) highlights that there are challenges in doing this for example time, commitment, financial resources, flexibility and patience; however (Gilbert, 2004) outlines benefits for people with learning disabilities such as facilitating people to have accesses to published literature and allowing them to help shape research questions. Involving people with learning disabilities could help to assist participation in research from an early stage therefore improving recruitment.

## **Fragile X syndrome trial barriers**

Carrying out clinical trials in FXS holds several challenges. Due to the heterogeneous population there is potential for each subpopulation to have differential therapeutic responses, this alongside the lack of specific outcome measures means that it can be difficult to measure changes. Early clinical trials have highlighted three specific challenges; heterogeneity, lack of biomarkers and no specific sensitive outcome measures. (Jacquemont et al., 2014). Future clinical trials in FXS need to be designed in a way that tracks changes over a longer period of time looking at multiple symptom domains and perhaps stratifying patients according to FMR1 (Jacquemont et al., 2014)

A key paper when looking at patient and family barriers to clinical trial participation, specifically in FXS, came from the MIND institute in California (Chechi et al., 2014). This paper assessed motivational factors and barriers for participation of underrepresented minority children in clinical trials for FXS and other neurodevelopmental disorders. Whilst this study looked in detail at FXS it focused specifically on children, although no age range is specified. They carried out a survey which was administered only to parents whose children were already attending the MIND institute for either treatment or to take part in research. The survey had twenty nine multiple choice questions which had additional space to provide further information. A total of one hundred responses were collected and analysed. A large focus was made on the reasons why people chose to or chose not to take part in clinical trials, for example low income families or age of child at time of diagnosis. They found the top two motivating factors for taking part in a clinical trial were to help find a cure and to help relieve symptoms related to a child's diagnosis. They reported a significant association between willingness to take part and; higher household income, and those whose children had been diagnosed earlier in life. The most common reason for choosing not to take part was requiring more information about side effects and

concerns over being given a placebo. No link was found between choosing to take part in clinical trials and gender, age, race and level of education.

It is therefore clear from the evidence that all clinical trials hold their own unique challenges and participants often are sceptical of experimental medicines. For example, concerns include the lack of assurance that they would not be given placebo, the potential for side effects, reluctance to devote the time needed to the clinical trial for additional appointments and procedures, and not being given enough information. These were also true when barriers specifically for FXS trials examined. Given the only study focusing specifically on barriers to clinical trial participation in FXS was done purely based on a survey of those already attending a single FXS clinic, there is a knowledge gap requiring more in-depth and generalisable information about barriers to participation and how these can be overcome. This may help make recommendations for future research study design, and thus improving the participation and providing clinical trials with the numbers required to make them a success.

## Chapter 3: Experiment



## **Introduction**

As reviewed in the previous chapter, recruitment to research studies for people with intellectual disabilities is a recognised struggle. Some work has been done to identify some of these challenges alongside strategies to overcome them (Lennox et al., 2005, Heller et al., 2014, Chechi et al., 2014, Ross et al., 1999, Oliver et al., 2002, Oliver-Africano et al., 2010). Only one of these studies related specifically to FXS and was conducted in a sample of individuals attending a single FXS clinic within a research centre in the USA.

Experience conducting research studies in FXS in our own research centre in the UK (the Patrick Wild Centre) has also suggested that recruitment to take part in clinical trials when testing new medications can be extremely challenging. Despite widespread circulation of information, there are a very limited number of families who contact the centre when they hear about clinical trials and many of those who do get in contact have concerns and reservations about participating.

It is important to fully establish what the patient and family associated barriers to participation are so that they can be addressed enabling successful recruitment to future clinical trials. It is notable that similar research conducted in prostate cancer trials showed that by integrating qualitative methods prior to randomised control trials, recruitment can be improved (Donovan et al., 2002). This study demonstrated that a simple identification of the core preventative barriers allowed trials to be tailored with these borne in mind and communication and recruitment strategies could be developed to address these head on.

## **Aims**

The primary aim of the study was to find out what prevents people with FXS from taking part in clinical trials.

The secondary aim of this study is to find out how barriers to clinical trial participation could be overcome amongst patients with fragile X syndrome and their families in order to maximise recruitment for future studies.

## **Research design**

A mixed method design was used, collecting both quantitative and qualitative data. A quantitative questionnaire was completed by parents, carers, family members of individuals with FXS or by people with FXS themselves. Following this, three focus groups took place in Chelmsford, Bristol and Edinburgh. All of the participants who took part in the focus group had taken part in the quantitative questionnaire.

Using both quantitative and qualitative methods for data collection meant that while it can be difficult to ensure complete objectivity during focus groups due to the subjective nature (Parahoo, 2014), validity and reliability could be sought from questionnaires.

## ***Quantitative methodology***

Quantitative research gathers numerical data to provide objective measurements which can be generalised across groups or people to explain a phenomenon. It was considered to be useful in this study to collect quantitative data as it allows responses from a larger number of people than could be sought from any other method. Using quantitative methods increases the application of findings to the wider population and allows a more accurate representation of the population. Using this method meant there was a greater degree of objectivity by avoiding variables and personal bias ensuring validity and reliability of results. Finally collecting quantitative data allowed data in the study to be easily summarised and comparisons made across the different questions asked.

### *Qualitative methodology*

Qualitative research aims to understand and make sense of individual's experiences by investigating meaning and significance thus allowing for a greater insight to the finer nuances of an individual's report and looking in greater detail at the person's understanding (Silverman, 2005). Use of a qualitative methodology allows a naturalistic and interpretive approach to systematically investigate human experiences, linking the patient's life and behaviour with their thoughts and feelings (Flick, 2009). It presumes that no objective conclusion can be ascertained, rather accepting that individuals will form their own subjective take from interactions, experiences and cultural norms (Denzin, 1984) and rejects the postmodernist concept of accepting knowledge as purely objective truth (Kvale, 1995). Qualitative research therefore facilitates a deeper insight into several different levels of knowledge which is unachievable using quantitative methods alone. The aim of this research was to find out what put people off taking part in previous clinical trials and to discover if there was anything that could be done for future clinical trials to make them more accessible for those who wish to take part. It was for this reason that a phenomenological research method was used as this method provides a rigorous, critical and systematic investigation of phenomena in order to capture individuals' experiences.

### *Phenomenology*

Phenomenology is used to describe phenomena, or appearance of things as lived experience (Cohen, 1987). It is a rigorous, critical and systematic method of investigation with lived experience as its central focus (Speziale et al., 2011). *"The purpose of phenomenological enquiry is to explicate the structure or essence of the lived experience of a phenomenon in the search for the unity of meaning which is the identification of the essence of phenomenon, and its accurate description through the everyday lived experience"* (Rose, 1990). As this study aims to understand people's reasons for not taking part in research and take into account their experiences of past research and

lived experience of having a child with FXS to see how barriers can be overcome, this was deemed to be the most appropriate research method. Purposeful sampling was used to select individuals with lived experience of FXS to take part.

## **Methods**

### ***Recruitment***

#### *General inclusion and exclusion criteria*

In order to participate in the study all individuals had to be over the age of 18. They had to be a family member or a carer of someone with a diagnosis of FXS. People with a diagnosis of FXS were included so long as they were able to read and write so they could complete the questionnaire. Both males and females were recruited. Individuals who could not read or write were excluded as they were required to complete the questionnaire without assistance from the research team. Only individuals who had completed the questionnaire were eligible to take part in a focus group. Written consent was collected from individuals who agreed to take part in the focus groups.

#### ***Ethical considerations***

Prior to this research being conducted it was presented to an external ethics committee for review. They granted favourable ethical opinion based on the submission of an application form along with a protocol and supporting documentation. This was granted on the 2<sup>nd</sup> of April 2015.

Implied consent was used for those taking part in the questionnaire (i.e. by completing and returning the questionnaire they were judged to have given consent). However for those wishing to take part in the focus groups fully informed consent was collected. All participants were informed that they could withdraw consent at any time without

being required to give an explanation. No payment was given for those who took part however all travel expenses were reimbursed to ensure that no participant was left out of pocket.

No benefits for taking part were anticipated, however participants were informed that information collected may lead to greater recruitment into clinical trials and that it could be possible the fragile x community could potentially benefit if new treatments are developed.

### *Identification/ approach*

The bulk of participants were identified by a member of the Fragile X Society from the UK Fragile X Society mailing list, which contains over 1000 families. The Fragile X Society was formed in 1990 by families whose children had been diagnosed with Fragile X Syndrome. They provide support and information to families affected by FXS from those who share and understand their concerns and needs. They educate and inform the public and professionals about FXS in order to raise awareness and understanding of the syndrome and so improve the care of all people affected by FXS and encourage research into all aspects of FXS and publicise the results.

The Society was involved in the early stages of the research project and in the development of the questionnaire to ensure they would be happy to support the study. They were provided with pre-made packs containing the questionnaire and a leaflet about the Patrick Wild Centre which meant the Society only had to add an individual's address to each envelope before they were sent out.

Furthermore, an email was sent using The Patrick Wild Centre mailing list to let people know about the study. All people on this mailing list were based in the UK and had given permission to be contacted with information regarding planned research

studies. This email was not targeted towards specific individuals but rather was sent to the mailing list as a whole.

The questionnaire was also advertised on the Patrick Wild Centre website, Facebook and Twitter feeds. When the study was posted on the Patrick Wild Centre Twitter page it was retweeted by seven different organisations and therefore returned responses from all over the world.

Participants were also identified by contacting people who have taken part in the fragile X registry project run by The Patrick Wild Centre who gave explicit permission to be contacted directly about future research.

At the end of the questionnaire participants were asked to provide their contact details if they wished to take part in a focus group. However, those who provided their contact details did not automatically get to take part in a focus group. Focus groups were run in locations with a sufficient number of interested individuals, to ensure there were enough people to take part. A minimum of 10 people were invited to attend each focus group.

### *Questionnaire*

The Questionnaire consisted of nine questions (see appendix 1). The questionnaire had the option to allow the participant to remain anonymous if they wished, however if they wanted to take part in the following focus group they had the option to leave their contact details. It was structured to ensure it took as little time as possible to complete to help encourage participation, by including as many tick box options as possible. There were boxes provided to give the option to provide further details if they wished to help collect as much specific data as possible.

Participants were asked about any previous clinical trial participation and their thoughts on taking part in future trials including any barriers that they perceived. This allowed for exploration of reasons why families may not consider taking part in clinical trials and what they thought could be done to help encourage participation. They were also asked what kind of experience they had to help contextualise the answers given in later questions. The Question 'Please tell us things that you feel would make it difficult for you or your family member to take part in research. Tick all of those that apply and please state any additional issues under "other" if they are not listed' was included to find out things that people might struggle with or find difficult that may lead to them choosing not to participate in a clinical trial.

It was available on both electronic and paper form to help maximise recruitment. The electronic version was set up on Survey Monkey and the settings prevented it from being filled out by the same person multiple times. A total of 1001 questionnaires were posted out to people who had consented to be informed about research projects through the Fragile X Society. The electronic version was emailed to members of the Patrick Wild Centre friends list and was also advertised on both the Fragile X Society and The Patrick Wild Centre twitter and Facebook pages.

### **Focus groups**

Focus groups were deemed to be the most appropriate method of data collection for the qualitative aspects of this project, as it was important to explore people's views and experiences in considerable detail and within a cocreative environment. It was thought that the group interaction in response to specific questions would provide valuable insights. The use of focus groups has become a popular approach in qualitative health research. A focus group refers to a group discussion in which the researcher actively encourages group interaction and ensures that participants talk amongst themselves rather than relying solely on the researcher (Barbour, 2008).

Focus groups *“tap into human tendencies. Attitudes and perceptions relation to concepts, products, services or programs are developed in part by interaction with other people. We are a product of our environment and are influenced by people around us”*(Krueger Richard and Anne, 1994) p10-11. While it has often been argued that phenomenology and focus groups are incompatible (Webb and Kevern, 2001), for this study a particular phenomenon is being looked at and the group process of a focus group provides a good platform for participants to shared lived experiences and how these may or may not impact on taking part in clinical trials. Focus groups can be particularly useful for addressing the ‘why not?’ questions and to obtain perspectives on topics which participants may have spent little time thinking about (Barbour, 2008).

Only people who completed the questionnaire were eligible to take part in focus groups. Three focus groups took place in locations picked based on where the maximum number to participants could be recruited in order to ensure as many people could participate. These were Chelmsford, Bristol and Edinburgh.

Prior to conducting focus groups informed consent was sought from all participants. Each participant was given a detailed information sheet (see appendix 2) which contained contact details for the person carrying out the study but also an independent contact who was not involved or would benefit from the study in any way so that independent non biased advice could be given if required. The information sheet was issued to inform participants about the purpose of the research including possible benefits and risks of taking part. This was both for the participants’ and researchers’ protection, and is important to protect the participant from receiving potential emotional, psychological and social harm that they may experience if they were not correctly informed (Gerrish and Lacey, 2010). At this time they were also given a copy of the consent form to read over to make sure they would be happy to take part. Subjects were informed that they had the right to withdraw at any time without giving a reason. After receiving the information sheet and consent form each



participant was then contacted by the researcher at least a week later to find out if they still wished to take part.

The author was trained in conducting focus groups by attending a course run by the Social Research Association (SRA) to ensure they had the necessary skills to conduct these to ensure quality and integrity of data collected. Although the material that was discussed was not particularly sensitive, there was a small chance that the focus groups would identify issues that the participant may have required support with. In this case, the facilitator was trained to handle the matter delicately and provide the individual with the opportunity to discuss the issue further out with the focus group. If any issues were identified that required further support then the investigators would signpost the person appropriately, provided the individual had provided consent (e.g. through the fragile X society support workers, or the person's GP).

### *Focus group topic guide*

To ensure the continuity of the focus groups and that all necessary topics would be covered, a topic guide was developed (see appendix 3) that drew on the data collected from the questionnaires. The topic guide was designed to allow for a flexible interview style using open ended questions and suggested clarification questions and probes to ensure that everything was covered whilst encouraging the groups to take an active role in forming the knowledge generated.

### *Rigour*

Reliability and validity are key concepts within qualitative research in order to establish veracity of findings. The criteria used to achieve these are credibility and transferability or generalisability.

### *Credibility*

Any study needs to be credible to ensure that the information being presented is believable and fits within the context of current literature and what is already known. In this study credibility was ensured by recruiting an appropriate sample. Other measures to ensure rigour include the following:

- During each focus group the facilitator used clarification throughout to ensure that the facilitator's understanding of what was said was correct.
- All groups were audio recorded and transcribed by an external agency (TP Transcriptions Ltd) to ensure that actual words spoken were easily accessible for analysis.
- After each focus group the contents of each group were discussed with a supervisor to reflect on findings and interpretation.

### *Transferability*

As focus groups were carried out by those willing and able to attend they may not constitute a truly representative sample. In order to improve transferability and generalisability the following measures were taken:

- The combination of quantitative data from the questionnaire alongside the focus groups provided evidence from a larger sample size.
- The participants who took part came from a range of backgrounds and geographical areas within the UK ensuring that the thoughts and experiences of a broad range of respondents were included.
- People were invited to take part in the focus groups who had said they would not consider taking part in research trials as well as those who said they would, to ensure a balanced group.

## *Reflexivity*

Reflexivity is an important part of qualitative research as the preconceptions and subjectivity of the researcher can bias or contaminate the data captured. It is therefore important to avoid losing richness of data which comes from the intersubjective interaction (Seale, 1999). By engaging in reflective practice it is therefore possible to recognise the effects of subjective processes within research and determine whether this has had an effect on the understanding and representation of the interviewer's subjective experience. While reflective practice has often been seen as self-indulgent and the emphasis often made on self-reflexivity (Riach, 2009, Finlay, 2002), being mindful of the processes and how preconceived epistemologies can influence research along with continual critique and awareness of the interviewer's position in the process of collecting the data. Each interview was recorded using a voice recorder however as this method is unable to capture facial expressions, interactions between focus group participants and general thoughts from the interviewer were recorded in a field note journal immediately after each session. This kept track of assumptions as well as emotional reactions (Gilbert, 2001) this was not only for the group but also for the observer, to enable understanding through self-reflection and avoid self-absorption (Lofland and Lofland, 2006, Kleinman and Copp, 1993). These notes were unable to be recorded during the focus groups as there was only one interviewer and taking notes may have disrupted the flow of conversation and there was a risk of the interviewer missing key parts of the discussion. A field note journal was used to aid analysis of the data and to reflect back on the interactions of the group including any potential influence by the interviewer over the discussion.

## *Data management*

On their return each questionnaire was allocated an identifying number for storage purposes. In most cases the questionnaire was anonymous, unless the participant

provided their contact details for the focus groups. In this case the identifiable information was detached from the questionnaire.

People who took part in the focus groups were allocated a unique code number to ensure confidentiality (Polit and Beck, 2004). A key to this code was kept in a locked filing cabinet separate from the data and consent forms. A further key was kept in a password protected file on a server that was only accessible through a password protected computer and which is distinct from the server where the data was held. This unique code number was used on all written data and any electronically held databases. Only the research team had access to this key to pseudonymise the data in order to prevent any breach of confidentiality. Any private data identifying participants was unable to be reported. The study adhered to the principles of Good Clinical Practice and all staff who worked on the study were trained appropriately.

## **Data Analysis**

### ***Quantitative analysis***

The analysis for the data obtained from the questionnaires was conducted using the IBM statistical package for social science (SPSS) (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). SPSS was used to run Pearson's Chi-squared tests to determine whether there were differences in the barriers identified between the two countries with the largest response rate and whether or not an interest in taking part in clinical trials made a difference to the barriers reported.

### ***Qualitative analysis***

Thematic analysis was used. Thematic analysis organises and describes data in detail and interprets various aspects (Braun and Clarke, 2006). This form of analysis was chosen due to its flexibility, allowing themes to emerge from the data rather than using a pre-existing theoretical framework. The recordings of the focus group were

transcribed by an external agency. While it is often thought to be important for the researcher to immerse themselves in the data and that the transcription process can be a good way to do this (Bird, 2005), it was felt that as the researcher carrying out analysis had facilitated the focus groups they had already begun familiarising themselves with the data so using an external agency would provide a more accurate transcription. The recordings were listened to by the researcher whilst reading the transcriptions several times prior to coding to help identify possible patterns and meanings, and to ensure data was accurately punctuated to ensure accuracy and that the meaning of data had not been altered (Gubrium and Holstein, 2002, Lapadat and Lindsay, 1999). This was used in conjunction with the field note journal kept for each focus group in order to assist recollections of the subtleties of the communication. Initial codes were then generated from the data. These codes were data driven and first performed manually and then Nvivo software (NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 10, 2012) was used to assist with the systematic analysis and to ensure accuracy. Once the data was coded potential themes were developed, this was done by both the researcher who facilitated the groups but also an external researcher to ensure reliability and validity. The themes were then reviewed together and refined after considering the validity of each theme in relation to the data set and a thematic map was created (see figure 3).

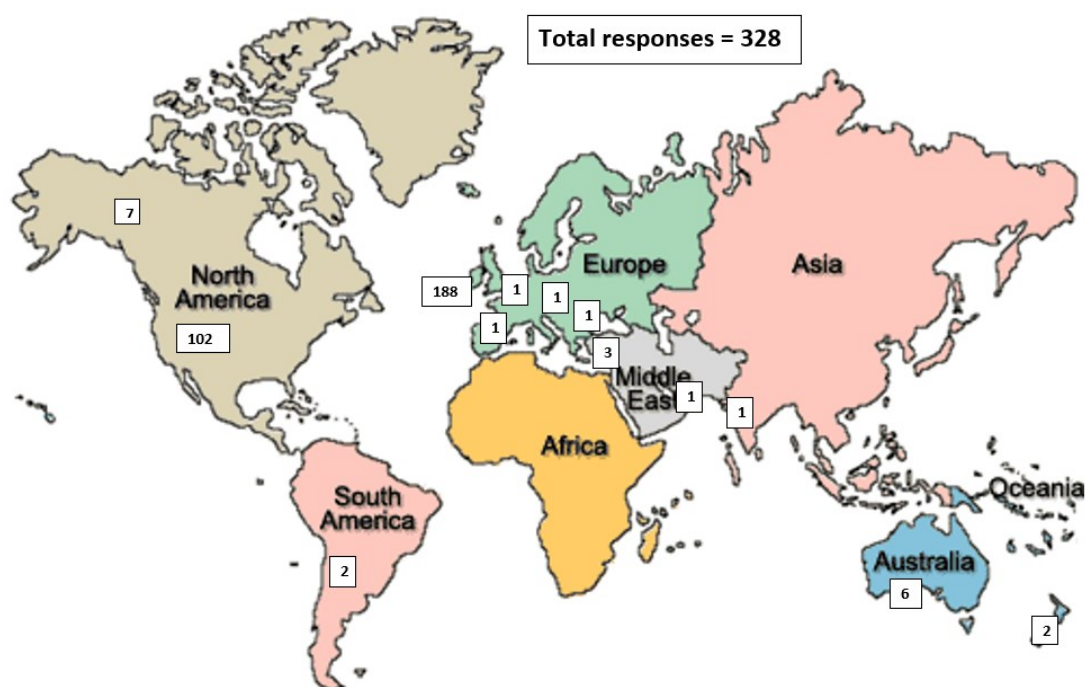
## **Chapter 4: Findings**

## Questionnaires

### *Participants*

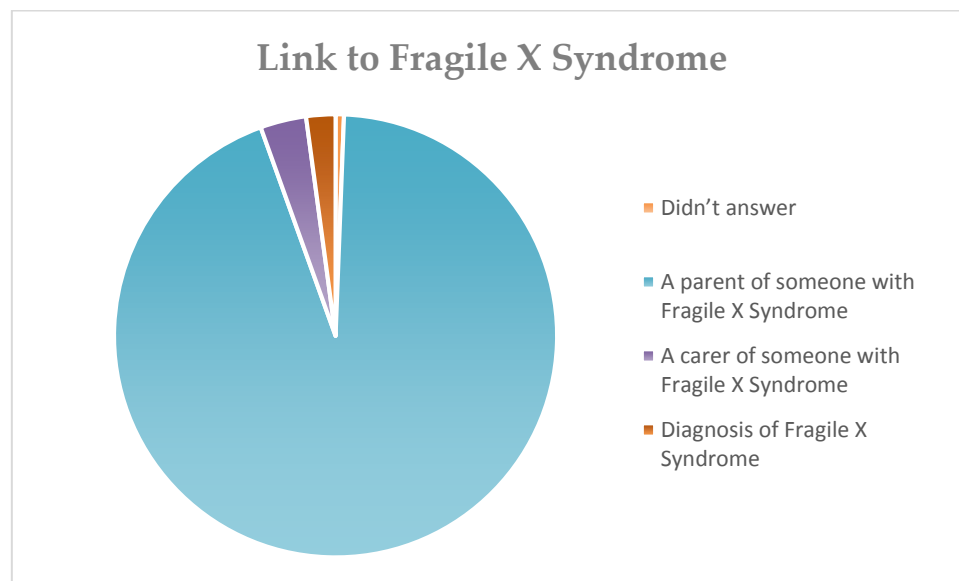
A total of 328 people completed the questionnaire. 148 people returned a paper version of the questionnaire and 180 completed it electronically. Figure 3 below shows the distribution of the number of results based on country completed. 90% of those who took part provided this information.

**Figure 3: Map demonstrating geographical distribution of responses**



Of the 328 people who took part, 94.5 were parents of a person with FXS, 3.37% were carers and 2.15% had a diagnosis of FXS (figure 4).

**Figure 4: Link to FXS**

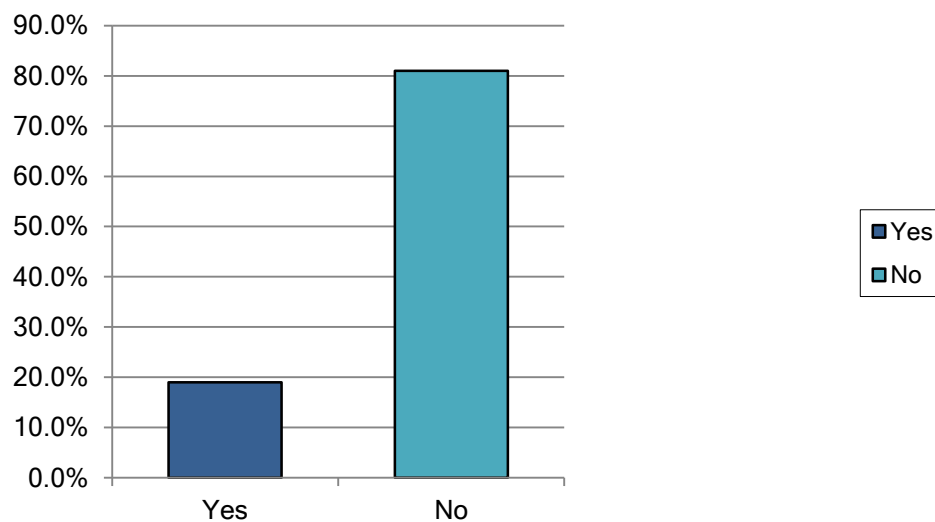


19% of people who completed the questionnaire had previously taken part in a trial of new medicines and 81% had not (figure 5). Of the people who had taken part in a previous trial 36.92% had a positive experience, 1.94% had a negative experience and 20.39% reported having a mixed experience. 41.7% of people did not complete this question (figure 6).

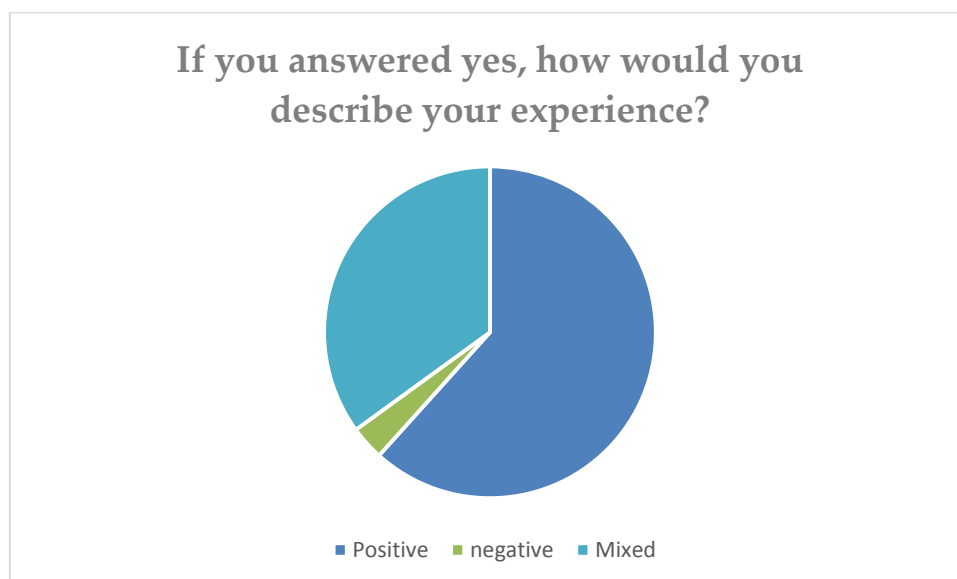


**Figure 5: previously taken part in a trial**

Have you or a member of your family taken part in trialling a new medication for Fragile X Syndrome?



**Figure 6: experience**



45.69% would consider taking part in future clinical trials, 42.49% would maybe consider taking part and 11.82% would not consider it (figure 7).

**Figure 7: Would take part in future trial**

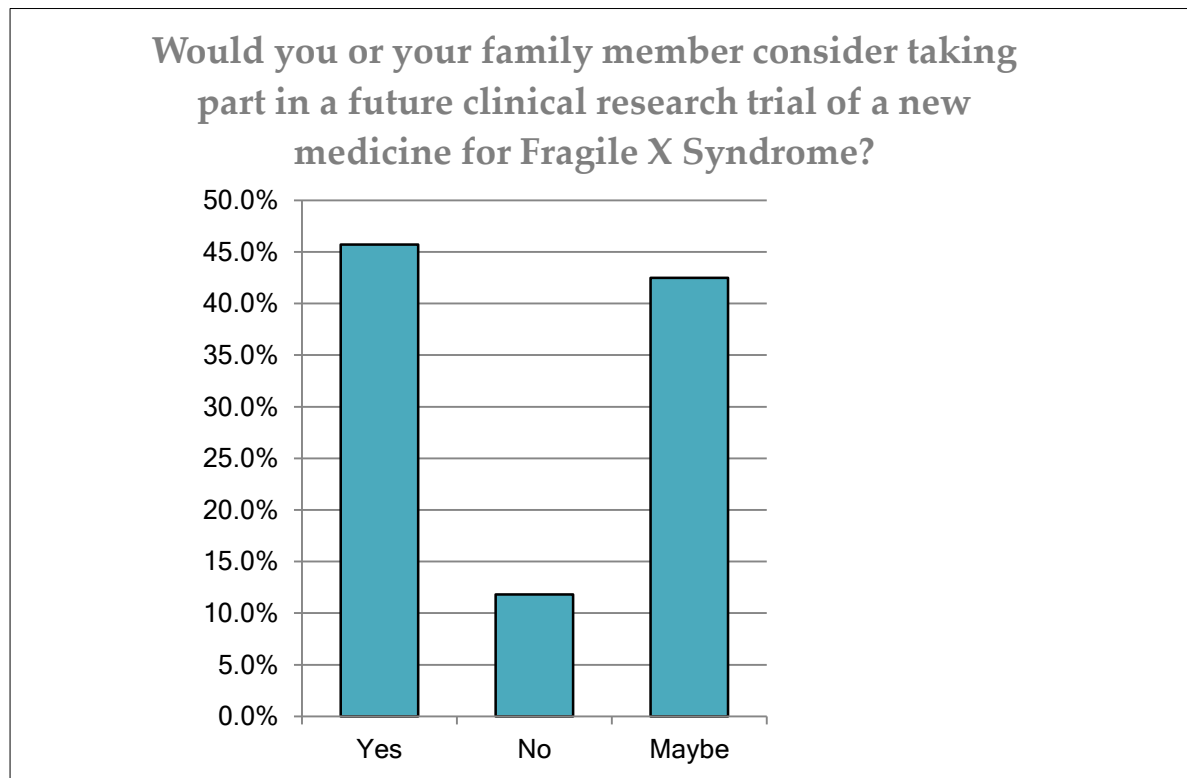
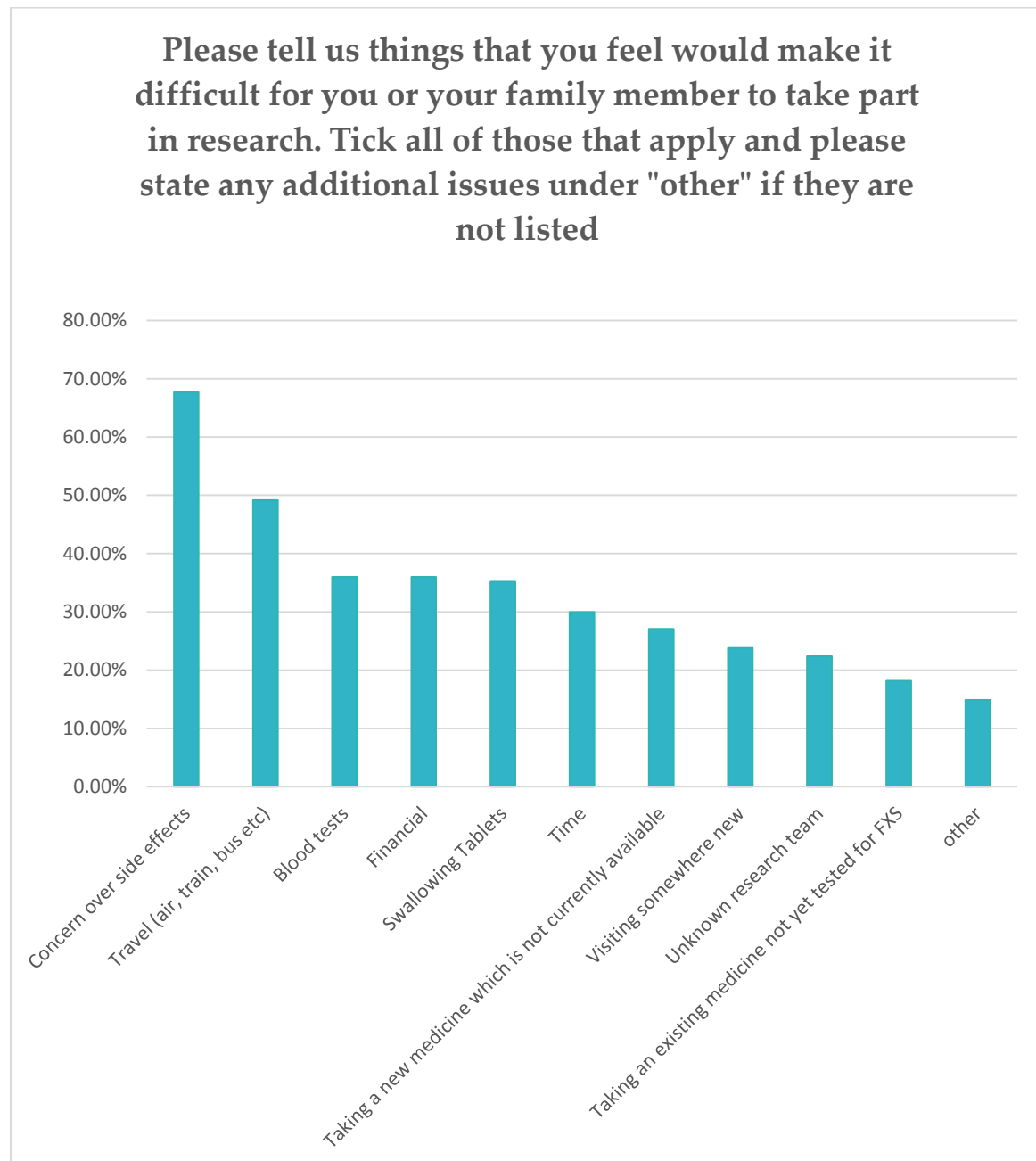


Figure 8 summarises the barriers to participation which were highlighted through the questionnaire. These barriers can be grouped into three categories: Drug effects, study procedures and effects of study on wider life. Over a fifth of participants reported swallowing tablets, financial aspects, blood tests and travel as barriers to participation and nearly 70% reported side effects as a barrier. Of those who ticked 'other' over 50% of these responses fall under current categories. 10% were concerned about seeing benefits from a trial then having to stop the medication and 5% would struggle to take part due to their child not living with them. 10 % of the comments were general trial comments unrelated to barriers and the remaining 20% covered things like disruption to routine, stress and not being aware of trials.

**Figure 8: Barriers to participation**



A large number of participants who completed the questionnaire were from the USA and this allowed a comparison between the UK and the USA to see if the different healthcare systems made a difference to the reported barriers. Table 1 reports these results. There were significant differences between the UK and USA on four barriers: a greater number of people in the UK felt taking an existing medicine which was not

approved for use in FXS, meeting an unknown research team and visiting a new place were barriers compared to those from the USA (all  $p < 0.05$ ), whereas a greater number of people from the USA felt that travel was a barrier to participation ( $p = 0.05$ ). Overall there seems to be more barriers reported from people in the UK.

**Table 1: USA v's UK barriers** (*significant results highlighted in bold*)

	UK	USA	Chi <sup>2</sup>	p
New medicine	24.4%	25.4%	.037a	.847
Existing medicine	22.7%	9.3%	8.853a	<b>.003</b>
Blood tests	38.6%	29.7%	2.500a	.114
Travel	42.6%	54.2%	3.829a	<b>.050</b>
Unknown research team	26.1%	14.4%	5.772a	<b>.016</b>
New place	29.0%	16.1%	6.455a	<b>.011</b>
Swallowing medication	37.5%	28.0%	2.875a	.090
Time	30.1%	28.0%	.157a	.692
Financial	30.7%	39.8%	2.622a	.105
Side effects	65.9%	61.0%	.733a	.392

Table 2 shows a list of barriers broken down to show the percentage of people who would consider, would maybe consider and who would not consider taking part in a clinical trial, to highlight whether certain barriers are more likely to put people off taking part in clinical trials completely. There was a significant difference between those who reported that they would or would not consider taking part in a clinical trial on six barriers (all  $p < 0.05$ ).

Those who said they would not participate more commonly reported that; taking a new medicine, taking an existing medicine not tested in FXS, blood tests, visiting a new place and side effects were barriers to participation, whereas those who said they would participate more frequently reported travel as a barrier.

**Table 2: barriers and willingness to participate** (significant results highlighted in bold)

	Yes	No	Maybe	Chi <sup>2</sup>	P
New medicine	13.3%	48.6%	33.1%	25.42	<b>&lt;0.001</b>
Existing medicine	7.0%	40.5%	22.6%	26.81	<b>&lt;0.001</b>
Blood tests	26.6%	40.5%	39.8%	6.26	<b>0.04</b>
Travel	43.4%	32.4%	54.9%	7.24	<b>0.03</b>
Unknown research team	17.5%	27.0%	24.8%	2.87	0.24
New place	16.1%	27.0%	29.3%	7.20	<b>0.03</b>
Swallowing medication	30.1%	29.7%	39.1%	2.83	0.24
Time	23.8%	35.1%	33.1%	3.64	0.16
Financial	31.5%	21.6%	39.8%	4.97	0.08
Side effects	55.9%	81.1%	69.2%	10.29	<b>0.006</b>

### Focus groups

A total of 182 people who completed the questionnaire provided contact details to be informed about taking part in a focus group. Of these 52 were contacted to take part. Focus groups took part in three locations throughout the UK to ensure as many people could take part as possible. The locations chosen were; Chelmsford, Bristol and Edinburgh. People who expressed interest in taking part who were not invited to take part were excluded based on living more than 70 miles from a focus group location. This was due to funding limitations. Of the people who took part 11 were parents, 1 was a carer and none of the participants had FXS. Focus groups were asked about their current understanding of clinical trials, what they would want to know before deciding whether or not for their dependant to take part in a clinical trial and also asked to imagine they were designing a clinical trial and what they would take into consideration (appendix 3). The table below outlines attendance to the focus groups (table 3).

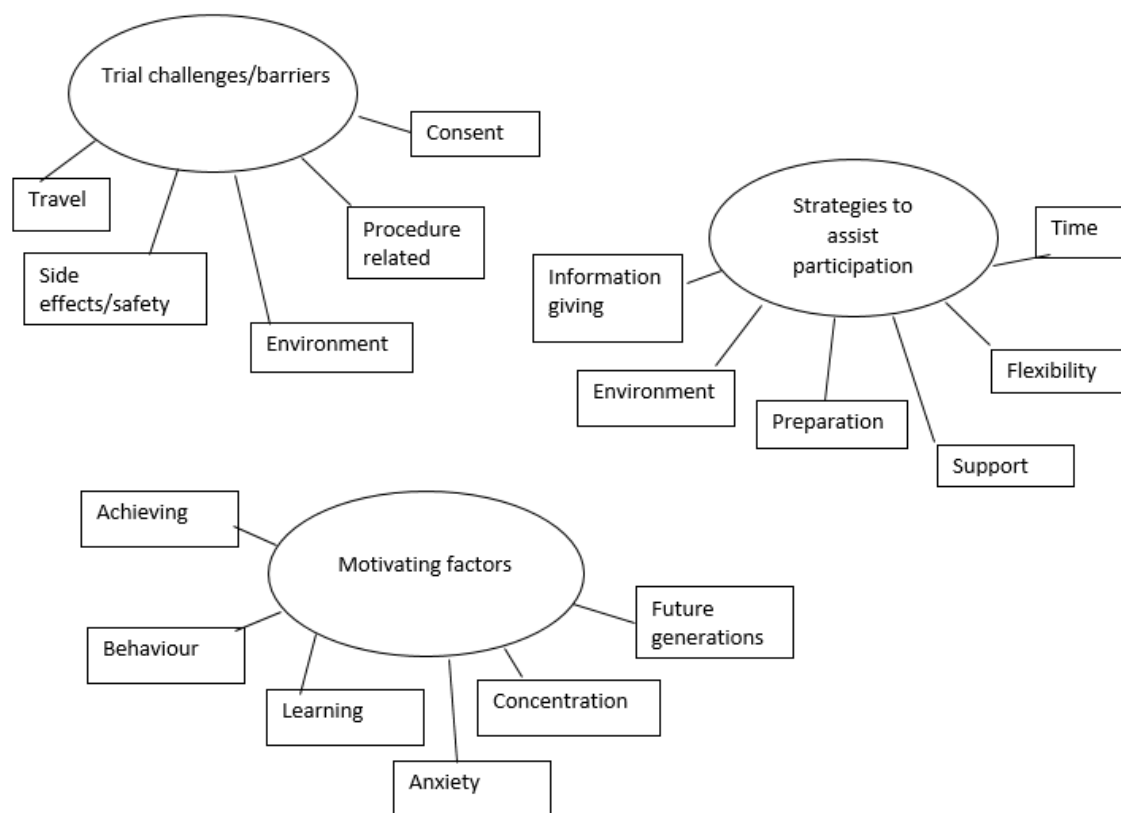
**Table 3: Focus group attendance**

Location	Number contacted	Number attended
Chelmsford	22	3
Bristol	19	6
Edinburgh	11	3

Data from the transcribed interviews was examined and was first split into 115 codes, which were then split into 6 categories and then grouped into themes with several sub themes. Much of the data overlapped between codes, categories and themes, however the process of assigning codes to different categories and then themes allowed exploration of the relationships amongst the issues arising from the data.

The three major themes that emerged from the data were: trial challenges/barriers, strategies to assist participation, and motivating factors. The main themes and sub themes identified following the coding are shown in a thematic map in figure 9, and each of the three themes are discussed in turn below.

**Figure 9: Thematic map**



### ***Theme 1 Trial challenges/ barriers***

In each focus group the participants were asked about specific barriers to taking part in FXS clinical trials and those mentioned were very much in line with what was reported in the questionnaire. Several sub themes were included in the theme trial barriers/ challenges and these are described in more detail below.

#### ***Travel***

There were varying degrees of how much of a barrier travel would be. The reason for travel being an issue was around the time it would take and the interruption to the patient's routine. This was particularly reported to be an issue if several research appointments were required:

*"It would have to be local"*

*"I don't have time to travel.. My boy loves travelling but we just can't afford the time"*

Focus groups mentioned very little difficulties with regards to their child's ability to travel on public transport or in a car, however it was alluded that this may not always be the easiest with one mother using sarcasm to show how difficult this can be:

*"Travelling with Fragile X is not, oh it's a joy (laughter)"*

It was mentioned in several of the focus group that given the option to travel together in a group would help to relieve some of the anxieties regarding this:

*"It would be friendly ...it would be an anxious situation but if you knew you were going to fly together and meet at the airport.."*

It was also mentioned that if the travel could be arranged for them so they did not have to organise it themselves, this would help to overcome travel as a barrier. For example, many people reported finding package holidays helpful, which arrange several aspects of travel for them when going on holiday:

*"I don't mind flying up but once I get to Edinburgh I think oh what do I do now? Because normally when I go on holiday you get all the pick-ups and they know where you are going and the hotel you are going to so it's all taken care of so you don't have to worry about it"*

### ***Procedure related difficulties***

There were many concerns raised in the groups around their children's ability to have their blood taken, being able to take medication and to cope with getting a scan. Many parents talked about previous experiences trying to give their child medications in different forms and discussed the need for researchers to have different options available:

*"My daughter will not and cannot take any medication in the form of tablets or medicine"*



Taking blood came up as a barrier in all three focus groups and was repeatedly brought up at different occasions throughout each group:

*"I nearly had my fingers broken while [child] has been having their blood taken"*

This is however not something parents would opt out of if the option was there as the safety of the trial outweighs the difficulty of the procedure, unless assurances were not given about why the blood test was in the protocol in the first place and if it was not vital for the trial:

*"They are important so I am not sure they could be reduced in a trial"*

*"I think they need to tell you why they do the blood tests then you would know"*

### ***Side effects/safety***

As demonstrated from the quantitative element of the research, the safety of the patient is a significant potential barrier to participation in any clinical trial. In fact for a majority, this is the single most important factor in consideration. The focus groups brought this issue to light in even greater detail. From the very beginning of the session there was widespread agreement that the potential side effects and toxicity of new medication is of primary concern. As one participant stated when asked what their primary concerns were:

*"Safety is number one"*

Another participant took this further to comment on the drugs themselves when used in clinical trials:

*"I am very very wary of the toxicity"*

As previously mentioned this highlights the need to ensure that these concerns are addressed from the outset of any clinical trial.

One participant commented on the issues they had had in previous trials that have had a knock on impact on future participation. The participant focused on a challenge which is specific to Fragile X Syndrome in terms of their child's inability to verbally express the issues she was experiencing, which for this participant was attributable directly to the trial drug itself:

*"[child] Non verbal...so when you're talking about drug trials... [child] would cry and you wouldn't know why"*

The overall concerns of new clinical trials in terms of side effects were effectively summarised by one participant who stated that:

*"I think a lot of people want to help but then they just don't know how their child is going to react"*

### ***Environment***

The environment relates to where the trial should take place. Each focus group was asked about trial locations for example clinics that were further away and would require travel, local clinics or trial visits taking place at home. Based on the questionnaires it was thought that as travel was one of the most common barriers and people would prefer to have visits completed at home, however this was not the case for everyone. A few participants felt it would be better to go somewhere else out with their home in case there were any negative consequences associated with the trial that they did not want to be associated with home:

*"I don't want home being associated with blood tests"*

There were some participants however that would favour trial being done in their own home as it would mean they did not have to travel and would take up less time. They also felt their child may be more relaxed:

*"I think it would have to be local familiar territory"*

*"Based at home would be nice"*

With regard to environment this overlapped with the issue of time, with many reporting they would need trials to take place more locally to fit in with their child's routine. The severity of the environment being a barrier related to how often the trial visits would take place:

*"They have to be local. It has to be out with school time"*

### **Consent**

As the majority of people attending the focus groups were parents to a child with Fragile X Syndrome one of the main concerns was over them consenting on behalf of their child. They felt if they could be of help they would take part in any trial that could potentially help their child however consenting on behalf of them to take part was a much bigger concern:

*"Saying yes for someone else is a big responsibility"*

*"Do whatever you want to me but my child is different"*

Whilst the parents understood that legally they were able to consent on behalf of their child they felt there was a big difference consenting on their behalf to take part in a drug study over other studies that do not involve medicines. Participants still felt that even for other studies that didn't involve new medicines consent can be tricky as their child with FXS wouldn't be able to understand why they would be taking part. Therefore consent may always be a struggle in all trials:

*"I don't think he would really understand why we were doing it so that's not informed consent is it?"*

*"I don't think he would understand what I was trying to explain to him"*

## *Theme 2 Strategies to assist participation*

The focus groups were asked about overcoming barriers and what they would like to know about before signing their dependant up to taking part in a clinical trial. They were also asked about what they would do if they were designing their own clinical trial to help with recruitment. The main subthemes which came out were; information giving, environment, preparation, support, flexibility and time.

### *Information giving*

The focus groups made it very clear that they wanted as much information on the trial medication as possible and having this information would help alleviate anxieties about side effects and safety. They also reported wanting very easy to understand and read information which breaks things up into chunks. It was suggested to have a short and long version so if someone was interested they can get more detailed information. Families specifically want to know what the medicine is trying to do:

*"I'd be happy if I knew that the side effects weren't going to be anything too major"*

The participants felt if they had lots of information about the trial medication and were made aware of previous safety trials and potential side effects then they could weigh these up and would be far more likely to participate:

*"..sign up for it straight away if something had already gone through safety trials"*

*"I'd have more worries about a completely new drug than one that's already been used and obviously the side effects were known"*

Many people reported wanting to meet the research team in person and have the opportunity to ask questions in an informal environment with the chance to listen to other people's questions. It was stressed that the researchers should use language that is easy to understand. They also felt this was important to build a trusting relationship with researchers. They recognised that perhaps it would not be possible for all people

to attend these events therefore it was important to use as many forms of media as possible to inform people about trials and specifically from a trusted source for example the Fragile X Society:

*"A table or stand at Society events... a face to face thing"*

*"Combination of all media"*

It was also reported that families did not necessarily feel they could contact the researcher to discuss the trial in more detail and that often they would see something in the information sheet and instantly dismiss the trial. Therefore having a line in the information sheet which explicitly says that researchers welcome families to contact them to talk about any concerns and how the trial could be made to work for them, would be beneficial:

*"I think families want to meet you and talk"*

### ***Environment***

Whilst environment was discussed under barriers to participation it was also felt that this could assist participation in clinical trials. Whilst talking about environment one of the participant commented:

*"We don't give our children enough credit for adapting to new things, they surprise you"*

They went on to say that this does not need to be a barrier and sometimes people with FXS surprise them by coping well with new places and situations, which opens doors to other new experiences that the family did not think were possible.

It was also mentioned that if trials take place in local places with local clinicians then this could be a real positive for the family as they would have a contact who knew their child and that their child felt comfortable around:

*“Local hospitals, local clinicians.. local clinicians getting to know them, actually that would be good for us”*

### ***Preparation***

Before taking part in a clinical trial many of the participants mentioned the importance of preparing their child to help them understand what they were going to be doing and why. It was discussed that if the trial team could provide easy to understand information they could share with their child that would be very beneficial:

*“A story board of what is going to happen”*

It was also highlighted that if their child got the preparation to get blood taken for the trial then this would be beneficial and make future routine tests at the doctors much easier:

*“Win win: you get the blood sample, we get a kid that is probably going to be able to give blood in the future”*

Participants also mentioned it would be beneficial for the trial team to provide packs specifically aimed at helping to overcome some of the things that their child may struggle with, for example education packs so parents can work through these with their child before attending clinic visits:

*“Education packs for kids so that they understand the process of taking blood”*

### ***Support***

In each group there was a positive discussion towards travelling to research appointments with other families to gain social support and have contact with families

in a similar situation to themselves. They also reported that this could help to reduce some of the stress of travelling:

*“With other families, they understand so I can just relax a bit”*

It was mentioned that travelling with others would not only take away the stress, but would also be a good opportunity to get social support from other families who understand, which families don’t always feel that they have time for:

*“you could get a minibus , you could make friends locally”*

*“it would be a real draw”*

*“with other families they understand so I can just relax a bit”*

### ***Flexibility***

Flexibility of the trial was mentioned frequently. Participants discussed in particular the barrier of their child’s ability to take medication, however if there was more flexibility and the trial drug could be given for example via a patch, liquid or suppository this would make a big difference to whether or not their child could take part:

*“If it’s drugs, personalise the method of administration”*

It was also suggested that being flexible with trial visit location would be helpful so doing some visits locally and only travelling for certain visits that were required to be done further afield:

*“You need a combination don’t you? You need something you do locally...then maybe a biannual trip further afield”*

Also being flexible with regards to the testing required could make a difference to whether or not someone would take part in a trial for example, taking blood in a different way such as using a finger prick sample, or if possible take samples less often:

*“Find a different way to get bloods that would be good”*

### ***Time***

It is important to take into account the distance to be travelled when designing the visit schedule as this can impact on the amount of time that is taken up by the trial. Families reported being happy enough to travel to a research appointment once every couple of weeks if the appointment was closer by but would only realistically manage a biannual trip if it was further away and required more time:

*“Within an hour’s travel might work”*

### ***Theme 3 motivating factors***

There were many different motivating factors for parents/carers wanting their dependant to take part in clinical trials however the same reasons were echoed in every focus group. There was a feeling of not wanting their child to change but rather to see improvements in certain areas of their lives such as anxiety, learning and concentration:

*“the biggest thing for my son is anxiety”*

*“anxiety and concentration”*

They wanted their child to be able to achieve more, not necessarily in school but rather to be able to go into social situations or crowded places without feeling uncomfortable to help them live a fuller life:



*“Anything that helps my daughter to be able to say her own name...anything that helps her achieve a bit more in life”*

The importance that clinical trials take place to further understand FXS and to help the next generation was echoed in each focus group:

*“Trials have to be looked at as positive”*

*“If we didn’t try things we wouldn’t get anywhere would we?”*

## **Chapter 5: Summary, discussion and future directions**

This chapter brings together both the quantitative and qualitative data from the study. Hypotheses and research questions will be discussed in depth and strengths and limitations from the study will be highlighted, including using two different methods of data collection. Implications for future practice will also be identified.

## **Discussion**

This study was conducted to identify barriers to clinical trial participation with families affected by fragile x syndrome and how these can be overcome. The study used both quantitative and qualitative methods to gather data. A mixed methods approach has not been used in previous research carried out in this area. Using a mixed methods approach was a way to add more depth to the data to explain why certain barriers exist and how families feel barriers can be overcome, or whether it is even possible to overcome barriers to research. Thus moving away from looking at barriers within the clinical setting that prevent participation and looking at the views from people who wish to take part but don't feel they are able to. The existing research suggests barriers to research participation in FXS include lack of information, side effects and concerns about being given a placebo and that people wanted to take part in trials in this field to help find a cure and to help relieve symptoms (Chechi et al., 2014). This study aimed to build on this research to find out if there were other barriers that had not been found previously, and perhaps identify country specific barriers as previous research has only been carried out in the United States of America. It also aimed to see if it was possible to overcome trial barriers and if so what the families think researchers could do to help increase participation.

## ***Barriers***

The primary aim of the study was to find out what prevents people with FXS from taking part in clinical trials. The study demonstrated clearly that there are many

different reasons for not taking part, however the main barriers to participation raised from the questionnaires were concerns about possible side effects, travel, requirement for blood tests and perceived or real financial reasons. When these barriers were explored further during focus groups it was evident that these barriers were not as clear as they may have initially appeared and had many complexities to them. The barriers from the study taking into account both quantitative and qualitative data can be split into three categories:

1. Drug effects: Taking a new medicine, taking an existing medication which has not be licenced in FXS and side effects.
2. Study procedures: blood tests, unknown research team, visiting a new place and swallowing medication.
3. Effects of study on wider life: Travel, time and financial

### **1. Drug effects**

Side effects were reported to be a barrier by 68% of the total sample, and 81% of those who said they would not currently consider taking part in a clinical trial because they were worried about side effects. Side effects were also reported in the literature to be one of the main barriers to participation in clinical trials more generally (Oliver-Africano et al., 2010, Ross et al., 1999, Chechi et al., 2014). With such a large proportion of people reporting that this particular barrier would prevent them from participating in research it was important to explore this further in the focus groups. The focus groups reported that there was great concern over side effects due to their child having difficulty reporting any side effects back to their family as a result of being non-verbal or having language difficulties. There was also concern that side effects may display themselves in other ways, such as behaviourally, and this could be distressing to families as they may not be able to tell if there was a problem or what the specific issue was. This was particularly a concern with some of the treatments that had severe side

effects such as hallucinations. The safety of the medications is paramount to families demonstrating the need for as much safety information to be available as possible.

Taking a new medicine was reported by 27% and taking an existing medicine which has not been licenced for use in FXS was reported by 18% of people who participated. While these were not some of the highest reported barriers they are highly significant when looking at whether people would or would not consider taking part in new clinical trials (table 2). If these were reported as the barriers to participation then they are less likely to take part in a future clinical trial with just under half of people who wouldn't take part in a future clinical trial reporting it as a barrier. As with side effects, this suggests that it is important to have as much information as possible on the medication so that people can make an informed choice.

## **2. Study procedures**

It appeared from the questionnaires that blood tests were a common trial barrier and on initial analysis that having blood tests in a trial would prevent people from taking part. It was surprising to find that when blood tests were discussed in the focus groups this was perhaps not such a deal breaker to participation as was initially thought. Taking blood was discussed as a challenge and something that people with FXS may struggle with, however it was not something that would solely put families off participating. Notably when discussed whether to have a choice to opt out of blood draws at study visits to increase participation this was met with caution from families who felt if an ethics committee had approved the protocol with blood tests in it then there would need to be assurances as to why it would be ok from some people not to have blood tests and still participate.

Taking part in a clinical trial with unknown research team and visiting a new place were highlighted by around a fifth of those who completed the questionnaire. These were not significant barriers in impacting on whether or not someone would or would

not take part in a clinical trial. Under 1/3 of people who wouldn't take part in a future trial reported these as being barriers. In focus groups families discussed that it would be preferred to meet the research team beforehand to build up a relationship and trust to help ease anxiety. It was also discussed if the research could be done by local clinicians this could provide a benefit to families as they would be able to make contact with people local to them and build up a relationship so in the future if there were any issues they would have a point of contact that their child felt comfortable visiting in a place that was familiar to them.

Swallowing medication was reported as a barrier by 35% of participants. The same percentage of people reported this as a barrier regardless of whether or not they would choose to take part in a future clinical trial. In focus groups different methods of medication administration were discussed as some people with FXS regardless of their age would not swallow any medication. Having flexibility as to administration method would allow more people to take part who wouldn't be able to if there was only a tablet form of medication. Suggestions given by families were an enema (as their child wouldn't be able to spit it out) or liquid form.

### **3. Effects of study on wider life**

The second highest reported barrier to participation was travel (49%). From the focus group discussions it became clear that travel was not simply about the mode of transport and associated anxiety but also included the time it takes, how often and possible interruption to routine. People reported that it was reasonable to travel short distances on a regular basis however would be willing to travel further if it was a couple of times a year. Families reported being anxious about travelling alone and how their child would feel about going on a plane or a train if they had never done this before but were open to the idea of trying it particularly if they could do this with other families who could provide peer support. It is interesting to note that while

travel was reported as one of the main barriers to participation, 44% of people who reported this to be a potential barrier would still consider taking part in a clinical trial.

As no research participant should ever be out of pocket for participating in research in the UK and with all travel expenses and meals being paid for by the study budget, looking at financial reasons as a barrier to participation was interesting to explore further. The results from the focus groups showed that this was a barrier due to being unaware that all research costs would be covered. The opinions of those who attended the focus groups showed that this was not as much of a barrier as it originally appeared and that the financial concerns they had regarding participation was more about having to take time off work. Very little time was spent discussing this barrier perhaps reflecting the results from the questionnaire which showed that this was more of a concern of people who completed it from the USA.

Time was reported by roughly a third of participants. People were concerned how much time travelling to research appointments would take and how many appointments they would need to attend. This was felt to be a barrier as they didn't want to interrupt their child's routine too much as they felt this could be disruptive. Interestingly they were not concerned about the length of time the research appointment itself would take.

### *Overcoming barriers*

The second aim of the study was to find out how barriers to clinical trial participation could be overcome. The study data acquired from the focus groups demonstrated clearly that there are many different ways that research teams can help to overcome barriers and make it easier for families affected by FXS to participate in clinical trials.

The main way to overcome barriers that came up repeatedly in each focus group was the importance of accessible information in helping families to understand the study including any potential safety issues in a variety of easy to understand formats. They felt a good way to get information on the study would be to meet the research team at information evenings and be given an opportunity to ask questions in an informal setting. Not only would this help alleviate anxiety about the study itself but would also be a good opportunity to meet the research team and build up a relationship with them helping to increase trust. The families suggested that if questions could be asked at an early stage that this could help to reduce anxieties and that families would be more likely to find a way to overcome perceived barriers in order to take part in a study.

Participants suggested travelling together in groups to provide peer support and to make it more of an event. Participants expressed that ideally research visits would take place nearby and at the most every couple of weeks. It was felt that many could realistically only manage a biannual appointment if the visits took place further from home. Therefore by adapting the study design to allow for this would help to improve participation by more families

Interestingly when the issue of blood tests was raised in focus groups families felt that they would not want to compromise safety for convenience and that they would rather withdraw from a study than continue without blood tests if these were felt to be necessary. Whilst interesting, this is somewhat of a moot point as regulators would not allow participants to continue in trials without adherence to the required safety blood testing schedule. Instead it was suggested by the families that a better way to overcome concern about phlebotomy would be to provide education packs in advance to prepare the participant with FXS for what would be involved in having their blood taken.



The study also found that a barrier to clinical trial participation was the result of a perceived lack of knowledge of trials taking place and as a result not enough known about them. Participants discussed their wish for wider advertisement of the trials through support groups, e.g The Fragile X Society, and online forums, as this was not something they would commonly seek out and search for themselves.

### *USA vs UK*

Looking at the data comparing the USA and the UK responses provides some insight into why some people reported certain barriers and whether there are UK or USA-specific barriers to participation. The data shows that people in the UK predominantly perceive there to be more barriers to taking part than those in the USA. The significant differences in perceived barriers are with regards to: taking an existing medicine, travel, meeting an unknown research team and visiting a new place (all  $p < 0.05$ ). These seem to be much more prominent concerns for respondents from the UK. Reasons for this may stem from the different health care systems; with higher baseline levels of psychotropic medication use and more frequent health care professional appointments in the USA as a result of more specialist clinics. A higher percentage of people in the USA reported travel and financial concerns as being potential barriers than those in the UK. We suspect that this is largely accounted for by the geographical differences of the country, with there being shorter distances required to travel for participants in the UK. Given that most studies include travel expenses for participants, it is not clear why those in the USA reported greater concern about financial burden; we speculate whether it may be related to the greater distance required to travel and thus the necessity for participants and their families to take leave from their paid employment in order to attend trial-related appointments. Both people in the UK and the USA reported concern about side effects to be the largest barrier to clinical trial participation. The focus groups emphasised that accessible

information and the ability to discuss concerns with the research team at an early stage would be potential ways to overcome this barrier.

This study highlights that while there are many things that can be done to help overcome barriers to participation there is not a fix that will work for all families. Researchers must look at ways to make their research more individual, flexible and accommodating. A positive outcome from the study is that 88% of people who completed the questionnaire said they either “would consider” or “would maybe consider” taking part in a clinical trial. This apparent appetite for participation highlights the need for researchers to make clinical trials more accessible to families by overcoming individual barriers that families may face. It is encouraging to note that of the 19% of people who had previously taken part in clinical trials only 2% reported having a negative experience. Advances in making research more accessible and enjoyable will hopefully mean that higher numbers will be able to take part in future clinical trials. Hopefully this will result in a greater range of intervention and treatment options available to individuals with FXS and their families.

## **Implications**

This study clearly shows the FXS clinical trials have a long way to go in reducing the barriers to participation to ensure those who wish to take part are able to. It is imperative that future researchers use what has been learnt in the study when designing future clinical trials in order to recruit the numbers needed for a successful trial. Potential trial modifications include:

1. Providing more information in accessible and easy to understand formats including safety data.

2. Holding information evenings where families can meet the research team and ask questions.
3. Provide the medication in different forms e.g enema or liquid as well as tablets.
4. Include as few blood draws as possible.
5. Consider the number of visits required for the study and the travel and time that would be required.
6. Provide story boards to help prepare people with FXS

### **Strengths and limitations**

The study benefits from having a large number of questionnaire responses collected worldwide and focus groups taking place in both Scotland and England ensuring a broad representation which helps to increase applicability while avoiding the possibility that findings are due to unusual local circumstances.

In addition, the study recruited mainly through the Fragile X society rather than being clinically derived, making this sample much more likely to represent the general FXS population than a clinic based sample.

A further strength of this study was using a mixed method approach. Using both quantitative and qualitative data provided a different perspective on the issues explored. The findings from both sets of data support each other, and taken together provide a more meaningful data set for how families feel future FXS clinical trials can be designed to support participation.

Despite people from 13 countries across 5 continents completing the study, the results are still limited by a relatively small sample size. It must be also acknowledged that the population taking part in the study are potentially biased towards those already

interested in research (as this was how the sample sent paper questionnaires were identified) and to those who are actively engaged with fragile x communities online. This potentially excludes those without internet access and who those who are not even thinking of participating in research. Thus, these results must be seen in the context of barriers to research who are at least already contemplative of participation in research.

A further limitation of this study was that small numbers attended two of the focus groups due to difficulties on the day or family commitments; although this shows the difficulties that families affected by fragile x syndrome face and further highlight the need for research to be made as easy as possible for them to participate in if families would like to do so.

Finally, trial barriers were suggested in the questionnaire therefore potentially influencing the responses given. However, the focus groups were carried out over 6 months after the questionnaire was completed which likely reduced the risk of participants from focusing on only the suggested barriers.

### **Future directions**

The findings from this study suggest many areas for further research in this area. One main area would be to further investigate trial barriers worldwide in order to determine whether the trial barriers found in this study relate in other areas of the world or whether the UK faces individual barriers.

Another interesting study to lead on from this work would be to examine the influence of participant characteristics on ability to take part in clinical trials. For example, whether having a child with different severities of FXS or a comorbid diagnosis, such as autism, has an impact on ability to participate in research and whether different

strategies would be required to improve participation. It may also be helpful with this to consider number of siblings and sibling diagnosis.

Case studies showing perspectives of families attitudes and perceived barriers before taking part in a clinical trial and then after having taken part would make for an interesting comparison and could potentially be very useful when informing families about future clinical trials.

Gaining information from people themselves with FXS to see how they feel about taking part in clinical trials and what they think researchers could do would provide an interesting and valuable insight to guide how future research could be carried out.

It would be useful to gain insights from clinicians and service providers to see what their opinions are of clinical trials of medicines in FXS and what the barriers would be for them to build on the work of (Oliver et al., 2002).

## **Conclusion**

It has been 73 years since FXS was first discovered and 50 years since testing for the condition has been widely used. In this time understanding of the biology and effects of the condition have improved and testing is more commonly carried out at an earlier stage in a child's development. However this increased knowledge has not transferred into the development of medication to help treat FXS specifically with many clinical trials failing to show improvement in primary outcome measures. The current study revealed that there are many things that researchers can do to help include participants in clinical research to help further examine new medicines for the condition.

## References

- ALLINGHAM-HAWKINS, D. J., BABUL-HIRJI, R., CHITAYAT, D., HOLDEN, J. J., YANG, K. T., LEE, C., HUDSON, R., GORWILL, H., NOLIN, S. L. & GLICKSMAN, A. 1999. Fragile X premutation is a significant risk factor for premature ovarian failure: the International Collaborative POF in Fragile X study—preliminary data. *American journal of medical genetics*, 83, 322.
- BARANEK, G. T., CHIN, Y. H., HESS, L. M. G., YANKEE, J. G., HATTON, D. D. & HOOPER, S. R. 2002. Sensory processing correlates of occupational performance in children with fragile X syndrome: Preliminary findings. *American Journal of Occupational Therapy*, 56, 538-546.
- BARBOUR, R. 2008. *Doing focus groups*, Sage.
- BEAR, M. F., HUBER, K. M. & WARREN, S. T. 2004. The mGluR theory of fragile X mental retardation. *Trends in neurosciences*, 27, 370-377.
- BERRY-KRAVIS, E., DES PORTES, V., HAGERMAN, R., JACQUEMONT, S., CHARLES, P., VISOOTSAK, J., BRINKMAN, M., RERAT, K., KOUMARAS, B. & ZHU, L. 2016. Mavoglurant in fragile X syndrome: Results of two randomized, double-blind, placebo-controlled trials. *Science translational medicine*, 8, 321ra5-321ra5.
- BERRY-KRAVIS, E. M., HESSL, D., RATHMELL, B., ZAREVICS, P., CHERUBINI, M., WALTON-BOWEN, K., MU, Y., NGUYEN, D. V., GONZALEZ-HEYDRICH, J. & WANG, P. P. 2012. Effects of STX209 (arbaclofen) on neurobehavioral function in children and adults with fragile X syndrome: a randomized, controlled, phase 2 trial. *Science translational medicine*, 4, 152ra127-152ra127.
- BILOUSOVA, T., DANSIE, L., NGO, M., AYE, J., CHARLES, J. R., ETHELL, D. W. & ETHELL, I. M. 2009. Minocycline promotes dendritic spine maturation and improves behavioural performance in the fragile X mouse model. *Journal of Medical Genetics*, 46, 94-102.
- BIRD, C. M. 2005. How I stopped dreading and learned to love transcription. *Qualitative inquiry*, 11, 226-248.
- BRAUN, V. & CLARKE, V. 2006. Using thematic analysis in psychology. *Qualitative Research in Psychology*, 3, 77-101.

- CAKU, A., PELLERIN, D., BOUVIER, P., RIOU, E. & CORBIN, F. 2014. Effect of lovastatin on behavior in children and adults with fragile X syndrome: an open-label study. *Am J Med Genet A*, 164A, 2834-42.
- CAMPBELL, S., ELEY, S. E., MCKECHANIE, A. G. & STANFIELD, A. C. 2016. Endocrine Dysfunction in Female FMR1 Premutation Carriers: Characteristics and Association with Ill Health. *Genes*, 7, 101.
- CHALELA, P., SUAREZ, L., MUÑOZ, E., GALLION, K. J., POLLOCK, B. H., WEITMAN, S. D., KARNAD, A. & RAMIREZ, A. G. 2014. Promoting Factors and Barriers to Participation in Early Phase Clinical Trials: Patients Perspectives. *Journal of community medicine & health education*, 4, 1000281.
- CHECHI, T., SIYAHIAN, S., THAIRU, L., HAGERMAN, R. & LOZANO, R. 2014. Participation of underrepresented minority children in clinical trials for Fragile X syndrome and other neurodevelopmental disorders. *Intractable & rare diseases research*, 3, 147.
- COHEN, M. Z. 1987. A historical overview of the phenomenologic movement. *Image: The Journal of Nursing Scholarship*, 19, 31-34.
- CORDEIRO, L., BALLINGER, E., HAGERMAN, R. & HESSL, D. 2011. Clinical assessment of DSM-IV anxiety disorders in fragile X syndrome: prevalence and characterization. *Journal of Neurodevelopmental Disorders*, 3, 57-67.
- CRAWFORD, D. C., ACUÑA, J. M. & SHERMAN, S. L. 2001. FMR1 and the fragile X syndrome: human genome epidemiology review. *Genetics in Medicine*, 3, 359-371.
- D'HULST, C. & KOORY, R. F. 2007. The GABA A receptor: a novel target for treatment of fragile X? *Trends in neurosciences*, 30, 425-431.
- DENZIN, N. 1984. Toward a Phenomenology of Domestic, Family Violence. *American journal of sociology*, 90, 483-513.
- DEPARTMENT OF HEALTH. 2000. *The NHS plan*. The stationery office. London.
- DEVITT, N. M., GALLAGHER, L. & REILLY, R. B. 2015. Autism Spectrum Disorder (ASD) and Fragile X Syndrome (FXS): Two Overlapping Disorders Reviewed through Electroencephalography—What Can be Interpreted from the Available Information? *Brain sciences*, 5, 92-117.

- DONOVAN, J., MILLS, N., SMITH, M., BRINDLE, L., JACOBY, A., PETERS, T., FRANKEL, S., NEAL, D. & HAMDY, F. 2002. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. *BMJ: British Medical Journal*, 325, 766.
- DZIEMBOWSKA, M., PRETTO, D. I., JANUSZ, A., KACZMAREK, L., LEIGH, M. J., GABRIEL, N., DURBIN-JOHNSON, B., HAGERMAN, R. J. & TASSONE, F. 2013. High MMP-9 activity levels in fragile X syndrome are lowered by minocycline. *American Journal of Medical Genetics Part A*, 161, 1897-1903.
- ERICKSON, C. A., MULLETT, J. E. & MCDOUGLE, C. J. 2010. Brief report: acamprosate in fragile X syndrome. *Journal of autism and developmental disorders*, 40, 1412-1416.
- ERICKSON, C. A., WINK, L. K., RAY, B., EARLY, M. C., STIEGELMEYER, E., MATHIEU-FRASIER, L., PATRICK, V., LAHIRI, D. K. & MCDOUGLE, C. J. 2013. Impact of acamprosate on behavior and brain-derived neurotrophic factor: an open-label study in youth with fragile X syndrome. *Psychopharmacology*, 228, 75-84.
- FARZIN, F., PERRY, H., HESSL, D., LOESCH, D., COHEN, J., BACALMAN, S., GANE, L., TASSONE, F., HAGERMAN, P. & HAGERMAN, R. 2006. Autism spectrum disorders and attention-deficit/hyperactivity disorder in boys with the fragile X premutation. *Journal of Developmental & Behavioral Pediatrics*, 27, S137-S144.
- FINLAY, L. 2002. Negotiating the swamp: the opportunity and challenge of reflexivity in research practice. *Qualitative research*, 2, 209-230.
- FLICK, U. 2009. *An introduction to qualitative research*, Sage.
- FORD, J. G., HOWERTON, M. W., BOLEN, S., GARY, T. L., LAI, G. Y., TILBURT, J., GIBBONS, M. C., BAFFI, C., WILSON, R. F. & FEUERSTEIN, C. J. 2005. *Knowledge and access to information on recruitment of underrepresented populations to cancer clinical trials*, Agency for Healthcare Research and Quality Rockville, MD.
- GARBER, K. B., VISOOTSAS, J. & WARREN, S. T. 2008. Fragile X syndrome. *European Journal of Human Genetics*, 16, 666-672.
- GERRISH, K. & LACEY, A. 2010. *The research process in nursing*, John Wiley & Sons.



- GILBERT, K. R. 2001. Why are we interested in emotions. *K. Gilbert, The emotional nature of qualitative research*, 3-15.
- GILBERT, T. 2004. Involving people with learning disabilities in research: issues and possibilities. *Health & social care in the community*, 12, 298-308.
- GUBRIUM, J. F. & HOLSTEIN, J. A. 2002. *Handbook of interview research: Context and method*, Sage.
- HAGERMAN, R., HOEM, G. & HAGERMAN, P. 2010. Fragile X and autism: intertwined at the molecular level leading to targeted treatments. *Mol Autism*, 1, 12.
- HAGERMAN, R., LAUTERBORN, J., AU, J. & BERRY-KRAVIS, E. 2012. Fragile X syndrome and targeted treatment trials. *Results Probl Cell Differ*, 54, 297-335.
- HAGERMAN, R. & POLUSSA, J. 2015. Treatment of the psychiatric problems associated with fragile X syndrome. *Current opinion in psychiatry*.
- HAGERMAN, R. J. & HAGERMAN, P. J. 2002. *Fragile X syndrome: Diagnosis, treatment, and research*, JHU Press.
- HELLER, C., BALLS-BERRY, J. E., NERY, J. D., ERWIN, P. J., LITTLETON, D., KIM, M. & KUO, W. P. 2014. Strategies addressing barriers to clinical trial enrollment of underrepresented populations: a systematic review. *Contemporary clinical trials*, 39, 169-182.
- HODAPP, R. M., DYKENS, E. M., HAGERMAN, R. J., SCHREINER, R., LACHIEWICZ, A. M. & LECKMAN, J. F. 1990. Developmental implications of changing trajectories of IQ in males with fragile X syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*, 29, 214-219.
- HUBER, K. M., GALLAGHER, S. M., WARREN, S. T. & BEAR, M. F. 2002. Altered synaptic plasticity in a mouse model of fragile X mental retardation. *Proceedings of the National Academy of Sciences*, 99, 7746-7750.
- HUNTER, J., RIVERO-ARIAS, O., ANGELOV, A., KIM, E., FOTHERINGHAM, I. & LEAL, J. 2014. Epidemiology of fragile X syndrome: a systematic review and meta-analysis. *Am J Med Genet A*, 164A, 1648-58.
- IRWIN, S. A., PATEL, B., IDUPULAPATI, M., HARRIS, J. B., CRISOSTOMO, R. A., LARSEN, B. P., KOOY, F., WILLEMS, P. J., CRAS, P. & KOZLOWSKI, P. B. 2001. Abnormal dendritic spine characteristics in

- the temporal and visual cortices of patients with fragile-X syndrome: a quantitative examination. *American journal of medical genetics*, 98, 161-167.
- JACQUEMONT, S., BERRY-KRAVIS, E., HAGERMAN, R., VON RAISON, F., GASPARINI, F., APOSTOL, G., UFER, M., DES PORTES, V. & GOMEZ-MANCILLA, B. 2014. The challenges of clinical trials in fragile X syndrome. *Psychopharmacology*, 231, 1237-1250.
- JACQUEMONT, S., HAGERMAN, R. J., LEEHEY, M. A., HALL, D. A., LEVINE, R. A., BRUNBERG, J. A., ZHANG, L., JARDINI, T., GANE, L. W. & HARRIS, S. W. 2004. Penetrance of the fragile X–associated tremor/ataxia syndrome in a premutation carrier population. *Jama*, 291, 460-469.
- KAUFMANN, W. E. & MOSER, H. W. 2000. Dendritic anomalies in disorders associated with mental retardation. *Cerebral cortex*, 10, 981-991.
- KIDD, S. A., LACHIEWICZ, A., BARBOUTH, D., BLITZ, R. K., DELAHUNTY, C., MCBRIEN, D., VISOOTSAK, J. & BERRY-KRAVIS, E. 2014. Fragile X syndrome: a review of associated medical problems. *Pediatrics*, 134, 995-1005.
- KIERNAN, C. 1999. Participation in research by people with learning disability: origins and issues. *British journal of learning disabilities*, 27, 43-47.
- KLAIMAN, C., QUINTIN, E. M., JO, B., LIGHTBODY, A. A., HAZLETT, H. C., PIVEN, J., HALL, S. S. & REISS, A. L. 2014. Longitudinal profiles of adaptive behavior in fragile X syndrome. *Pediatrics*, 134, 315-24.
- KLEINMAN, S. & COPP, M. A. 1993. *Emotions and fieldwork*, Sage publications Newbury Park, CA.
- KRUEGER RICHARD, A. & ANNE, C. M. 1994. Focus groups. A practical guide for applied research. Thousand Oaks: Sage.
- KVALE, S. 1995. The social construction of validity. *Qualitative inquiry*, 1, 19-40.
- LAPADAT, J. C. & LINDSAY, A. C. 1999. Transcription in research and practice: From standardization of technique to interpretive positionings. *Qualitative inquiry*, 5, 64-86.
- LEIGH, M. J., NGUYEN, D. V., MU, Y., WINARNI, T. I., SCHNEIDER, A., CHECHI, T., POLUSSA, J., DOUCET, P., TASSONE, F., RIVERA, S. M., HESSL, D. & HAGERMAN, R. J. 2013. A randomized double-blind, placebo-controlled trial of minocycline in children and adolescents with fragile x syndrome. *J Dev Behav Pediatr*, 34, 147-55.

- LENNOX, N., TAYLOR, M., REY-CONDE, T., BAIN, C., PURDIE, D. & BOYLE, F. 2005. Beating the barriers: recruitment of people with intellectual disability to participate in research. *Journal of Intellectual Disability Research*, 49, 296-305.
- LEVENGA, J., DE VRIJ, F. M., OOSTRA, B. A. & WILLEMSSEN, R. 2010. Potential therapeutic interventions for fragile X syndrome. *Trends in molecular medicine*, 16, 516-527.
- LOFLAND, J. & LOFLAND, L. H. 2006. *Analyzing social settings*, Wadsworth Publishing Company Belmont, CA.
- LUBS, H. A. 1969. A marker X chromosome. *American Journal of Human Genetics*, 21, 231.
- MAES, B., FRYNS, J.-P., GHESQUIÈRE, P. & BORGHGRAEF, M. 2000. Phenotypic checklist to screen for fragile X syndrome in people with mental retardation. *Mental retardation*, 38, 207-215.
- MARTIN, J. P. & BELL, J. 1943. A pedigree of mental defect showing sex-linkage. *Journal of neurology and psychiatry*, 6, 154.
- OLIVER-AFRICANO, P., DICKENS, S., AHMED, Z., BOURAS, N., COORAY, S., DEB, S., KNAPP, M., HARE, M., MEADE, M., REECE, B., BHAUMIK, S., HARLEY, D., PIACHAUD, J., REGAN, A., ADE THOMAS, D., KARATELA, S., RAO, B., DZENDROWSKYJ, T., LENOTRE, L., WATSON, J. & TYRER, P. 2010. Overcoming the barriers experienced in conducting a medication trial in adults with aggressive challenging behaviour and intellectual disabilities. *J Intellect Disabil Res*, 54, 17-25.
- OLIVER, P., PIACHAUD, J., DONE, J., REGAN, A., COORAY, S. & TYRER, P. 2002. Difficulties in conducting a randomized controlled trial of health service interventions in intellectual disability: implications for evidence-based practice. *Journal of Intellectual Disability Research*, 46, 340-345.
- OSTERWEIL, E. K., CHUANG, S.-C., CHUBYKIN, A. A., SIDOROV, M., BIANCHI, R., WONG, R. K. & BEAR, M. F. 2013. Lovastatin corrects excess protein synthesis and prevents epileptogenesis in a mouse model of fragile X syndrome. *Neuron*, 77, 243-250.
- PARAHOO, K. 2014. *Nursing research: principles, process and issues*, Palgrave Macmillan.
- POLIT, D. F. & BECK, C. T. 2004. *Nursing research: Principles and methods*, Lippincott Williams & Wilkins.

- POP, A. S., GOMEZ-MANCILLA, B., NERI, G., WILLEMSSEN, R. & GASPARINI, F. 2014. Fragile X syndrome: a preclinical review on metabotropic glutamate receptor 5 (mGluR5) antagonists and drug development. *Psychopharmacology (Berl)*, 231, 1217-26.
- REISS, A. L. & FREUND, L. 1992. Behavioral phenotype of fragile X syndrome: DSM-III-R autistic behavior in male children. *American journal of medical genetics*, 43, 35-46.
- REISS, A. L. & HALL, S. S. 2007. Fragile X syndrome: assessment and treatment implications. *Child and adolescent psychiatric clinics of North America*, 16, 663-675.
- RIACH, K. 2009. Exploring participant-centred reflexivity in the research interview. *Sociology*, 43, 356-370.
- RILEY, K. 2011. Infusing etiology into intervention: a model for translational research in education. *International Review of Research in Developmental Disabilities*, 261-292.
- ROSE, J. F. 1990. Psychologic health of women: A phenomenologic study of women's inner strength. *Advances in Nursing Science*, 12, 56-70.
- ROSS, S., GRANT, A., COUNSELL, C., GILLESPIE, W., RUSSELL, I. & PRESCOTT, R. 1999. Barriers to participation in randomised controlled trials: a systematic review. *Journal of clinical epidemiology*, 52, 1143-1156.
- SABARATNAM, M. 2006. Fragile-X syndrome. *Psychiatry*, 5, 325-330.
- SEALE, C. 1999. Quality in qualitative research. *Qualitative inquiry*, 5, 465-478.
- SILVERMAN, D. Instances or sequences? Improving the state of the art of qualitative research. Forum Qualitative Sozialforschung/Forum: Qualitative Social Research, 2005.
- SONG, F., BARTON, P., SLEIGHTHOLME, V., YAO, G. & FRY-SMITH, A. 2003. Screening for fragile X syndrome: a literature review and modelling study.
- SPENCER, C., ALEKSEYENKO, O., SERYSHEVA, E., YUVA-PAYLOR, L. & PAYLOR, R. 2005. Altered anxiety-related and social behaviors in the Fmr1 knockout mouse model of fragile X syndrome. *Genes, Brain and Behavior*, 4, 420-430.
- SPENCER, C. M., GRAHAM, D. F., YUVA-PAYLOR, L. A., NELSON, D. L. & PAYLOR, R. 2008. Social behavior in Fmr1 knockout mice carrying a human FMR1 transgene. *Behavioral neuroscience*, 122, 710.

- SPEZIALE, H. S., STREUBERT, H. J. & CARPENTER, D. R. 2011. *Qualitative research in nursing: Advancing the humanistic imperative*, Lippincott Williams & Wilkins.
- SUTHERLAND, G. R. & HECHT, F. 1985. *Fragile sites on human chromosomes*, Oxford.
- SZKLARCZYK, A., LAPINSKA, J., RYLSKI, M., MCKAY, R. D. & KACZMAREK, L. 2002. Matrix metalloproteinase-9 undergoes expression and activation during dendritic remodeling in adult hippocampus. *The Journal of neuroscience*, 22, 920-930.
- TSIOURIS, J. A. & BROWN, W. T. 2004. Neuropsychiatric symptoms of fragile X syndrome. *CNS drugs*, 18, 687-703.
- TURK, J. 2011. Fragile X syndrome: lifespan developmental implications for those without as well as with intellectual disability. *Current opinion in psychiatry*, 24, 387-397.
- VERKERK, A. J., PIERETTI, M., SUTCLIFFE, J. S., FU, Y.-H., KUHL, D., PIZZUTI, A., REINER, O., RICHARDS, S., VICTORIA, M. F. & ZHANG, F. 1991. Identification of a gene (< i>FMR</i>-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell*, 65, 905-914.
- WALMSLEY, J. 2001. Normalisation, Emancipatory Research and Inclusive Research in Learning Disability. *Disability & Society*, 16, 187-205.
- WEBB, C. & KEVERN, J. 2001. Focus groups as a research method: a critique of some aspects of their use in nursing research. *Journal of advanced nursing*, 33, 798-805.
- YUHAS, J., CORDEIRO, L., TASSONE, F., BALLINGER, E., SCHNEIDER, A., LONG, J. M., ORNITZ, E. M. & HESSL, D. 2011. Brief report: Sensorimotor gating in idiopathic autism and autism associated with fragile X syndrome. *Journal of autism and developmental disorders*, 41, 248-253.

## Appendix 1: Questionnaire



Kennedy Tower  
Royal Edinburgh Hospital  
Edinburgh  
EH10 5HF

Dear family,

Enclosed is a short survey asking about your feelings on taking part in research for people affected by Fragile X. It would be great if you could fill out the survey (shouldn't take longer than 5 minutes) and send it back to us in the freepost envelope.

The reason we are asking families to do this is to give us an idea about how people feel about taking part in research into new medicines for Fragile X. We want to make it easier for people with Fragile X and their families to work with researchers in the future. Experience conducting research studies in fragile X syndrome has suggested that some families are reluctant to take part in clinical trials of new medications. If numbers cannot be sought for these trials then clinicians are less likely to fund or use interventions. We aim to identify barriers to research participation in order to maximise recruitment to future studies.

Our team at the Patrick Wild Centre aims to improve understanding of Fragile X syndrome in order to help improve outcomes for those affected. We have enclosed a leaflet to tell you a bit more about what we do.

To achieve this, we really need the involvement and support of people with Fragile X and their families. Please take part in this survey so we can find out more about your needs and opinions on research.

We would be really grateful for your help with this survey.

Kind Regards

Sarah Wright

Patrick Wild Centre Liaison Nurse

Dr Andrew Stanfield

Director of the Patrick Wild Centre

**Identifying barriers to clinical trial participation with families affected by fragile X syndrome (IBX)**

County/ region of residence:

Are you

- ☐ A parent of someone with fragile X?
- ☐ A carer of someone with fragile X?
- ☐ Do you have fragile X syndrome?

Have you or a member of your family taken part in trialling a new medication for Fragile X Syndrome?

Yes/No

If yes; How would you describe your experience?

Positive/negative/mixed

Please give details

Would you or your family member consider taking part in a future clinical research trial of a new medicine for Fragile X?

Yes / No/ maybe

Please give details about your answer

Please tell us things that you feel would make it difficult for you or your family member to take part in research. Tick all of those that apply and please state any additional issues under “other” if they are not listed

- ☐ Taking a new medicine which is not currently available
- ☐ Taking an existing medicine which has not been specifically approved for Fragile X syndrome
- ☐ Blood test
- ☐ Travel (air, train, bus etc)
- ☐ Unknown research team
- ☐ Visiting somewhere new
- ☐ Swallowing tablets
- ☐ Time
- ☐ Financial
- ☐ Concern over side effects
- ☐ Other

Please provide further details

Please tell us things that you think would encourage people to take part in trials of new medicines



Do you have any worries or fears about you or your family member taking part in trials of new medicines?

Yes/No

If yes please detail below

If there was a new treatment (medicine or otherwise) available for fragile X syndrome, what would you most like it to help with? (e.g. these could be certain behaviours, learning abilities or anything else)

We would like to thank you for your time taken to complete this Survey it is very much appreciated.

Following on from this Survey we would like to ask families and carers to take part in small group discussions to explore key points further. If you would like to be considered for this please provide contact details below.

Name: \_\_\_\_\_

Email: \_\_\_\_\_

Phone  
number: \_\_\_\_\_

Address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

## Appendix 2: Information sheet



### Participant Information Sheet

#### Identifying barriers to clinical trial participation with families affected by fragile X syndrome

You are being invited to take part in a focus group as part of a research study. Before you decide whether you would like to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you would like to take part.

#### What is the purpose of the study?

The reason we are asking families to do this is to give us an idea about what stops people taking part in research of new medicines. We want to make it easier for people with Fragile X and their families to work with researchers in the future.

#### Why have I been invited to take part?

You have been asked to take part as you indicated on the questionnaire that you filled out previously that you would like to be considered to take part.

#### Do I have to take part?

It is up to you to decide whether or not you wish to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide that you will take part you are still free to withdraw at any time and without giving a reason. If you choose to withdraw from the study identifiable data already collected may be retained and used for the study.

#### What will happen if I take part?

You will be invited to attend one of the focus groups that we are running throughout the UK. The focus group will consist of around eight people should last roughly 45 minutes. At the start of the focus group you will be asked to complete the consent form and will be given an opportunity to ask any questions you may have. The group

facilitator will bring up broad key themes from the questionnaires and invite you to discuss these in more detail. The focus group will be recorded and then transcribed to allow the discussions to be accurately analysed. The transcription will be completed by an experienced transcription service who confirm that information will be kept strictly confidential.

### **What will I have to do?**

You will be invited to discuss themes that have been brought up from the questionnaires. It will be up to you how much detail you wish to go into and how much you wish to disclose.

### **What are the possible benefits of taking part?**

We do not anticipate that this study will benefit participants directly. However, it may help us to design better future trials and are easier to take part in. Should it lead to greater recruitment into clinical trials, it is possible that the fragile X community will benefit if new treatments are developed.

### **What are the possible disadvantages and risks of taking part?**

You will be required to give up your time to travel for the research and also the time taken to participate.

Although the material to be discussed is not particularly sensitive, there is a small chance that the focus groups may identify issues that you may find upsetting.

### **What happens to the information collected?**

The information we collect will be stored in paper form and on a secure computer at the University of Edinburgh. We allocate a secret code number so that if anyone saw this information they would not recognise them. The key to this code is kept separately from the data.

All the information we collect during the course of the research will be kept strictly confidential and there are strict laws which safeguard your privacy at every stage. Sometimes we may want to share the data collected with other medical and scientific researchers. In these cases, we do not share any identifiable information like their name and address, so the people we share the data with would not be able to recognise you from it.

### **Will you be paid for taking part?**

We will not pay you for your time but we cover any travel expenses or food that you have bought when coming to see us.

## **What will happen to the results of the research study?**

We will write up the results from the study as a publication. This will be in a specialist medical journal. We will also write a report for the Fragile X Society newsletter and present the findings at various conferences. However, your personal details will not appear in any report or publication arising from the research.

## **Will my taking part in the study be kept confidential?**

All the information we collect will be kept strictly confidential and there are strict laws which safeguard your privacy at every stage. If you choose to take part in a focus group you will be allocated a unique code number which will not be shared with anyone outside the research team.

## **Do the study investigators make any money from my participation?**

The study investigators are not paid anything for including you in the study, other than their ordinary salary.

## **Who has reviewed the study?**

The study has been reviewed by the local Research Ethics Committee.

**If you have any further questions about the study you can discuss them with Sarah Eley who is running the study (0131 537 6673 or [s.eley@ed.ac.uk](mailto:s.eley@ed.ac.uk))**

**If you wish, you could contact Professor Stephen Lawrie (0131 537 6671) who is not involved with this study and could give impartial information about it.**

If you wish to make a complaint about the study please contact the University of Edinburgh's Research Governance team via email at:  
[researchgovernance@ed.ac.uk](mailto:researchgovernance@ed.ac.uk)

## **Appendix 3: topic guide**

### **Barriers to clinical trial participation**

#### **Topic guide**

- **confidentiality**
- **Take turns, listen, be respectful**

#### **Introduction (10 mins)**

- Want to find out what you know
- Want to work with you to better design clinical trials
- tell me a bit about yourself – your name and why you were interested in coming along
- tell me about your child with FXS

#### **If I say ‘clinical trial’ what does that make you think? (10mins)**

- Write down the first 3 things that come into your head

*From this point on when we talk about clinical trials we are talking about trials of new medicines*

#### **If we were to ask you to take part in a clinical trial what sort of things would you want to know about?(15mins)**

- How would you hear about it?
- Specific barriers
  - What could be done to make you more comfortable about that?
  - What are your views and thoughts on that?
  - What’s the most important?
- Opportunities/potential benefits?
  - Most important

#### **Imagine you woke up tomorrow and you were in a team designing a clinical trial what sort of things would you be thinking about? (15mins)**

- How would you let people know?
- What would you do to encourage people?
- What would it help with?